FDA Introductory Remarks

Endocrinologic and Metabolic Advisory Committee (EMDAC) Meeting

May 24, 2015

NDA# 208583

Regulations for Combination Drugs

- Defined in Title 21 of the Code of Federal Regulations (21 CFR 300.50)
- Each component in the combination drug must contribute to the claimed effects
- The claimed effect for an antidiabetic is “is an adjunct to diet and exercise to improve glycemic control” (captured using HbA1c changes)
- Improvement in glycemic control is used as a surrogate for clinical benefit

Contribution to Claimed Effects

- ***Factorial Study:*** Tests the glucose lowering effect of two components versus individual components

  For a given dose of drug A and drug B

  HbA1c reduction for [A+B] is greater than for component [A] alone

  HbA1c reduction for [A+B] is greater than for component [B] alone

- ***Add-on Study:*** Tests the glucose lowering effect of adding a second drug to a maximally effective dose of a first drug in patients inadequately controlled on a first drug at baseline

  HbA1c reduction for [First + Second Drug] is greater than for [First drug + PBO]

Applicability to the Care Setting

- ***Factorial Study:*** Initiating two drugs at once versus each drug separately
- ***Add-on Study:*** Initiating a second drug only when a first drug is inadequate to control glucose

Does the Product Meet the Need?

- *"The dosage of each component (amount, frequency, duration) is such that combination drug is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug"*
- **Is the general concept rational?**
  - Are the two drugs available and already used concurrently for the treatment of the disease? If so, in whom and at what doses? Has concurrent use already been established to be safe and effective for the individual products?
- **Given the specific limitations of the product, is it still rational?**
  - Would the combination **product** be safe and effective for a significant patient population requiring such concurrent therapy?

Proposed Antidiabetic Combination

- The proposed combination drug in this application combines two already marketed "active ingredients" (i.e., drug substances)
  - Degludec; a basal insulin injected once daily
  - Liraglutide; a GLP-1 receptor agonist also injected once daily
- Insulins and GLP-1 receptor agonist are used concurrently in some patients for the treatment of type 2 diabetes

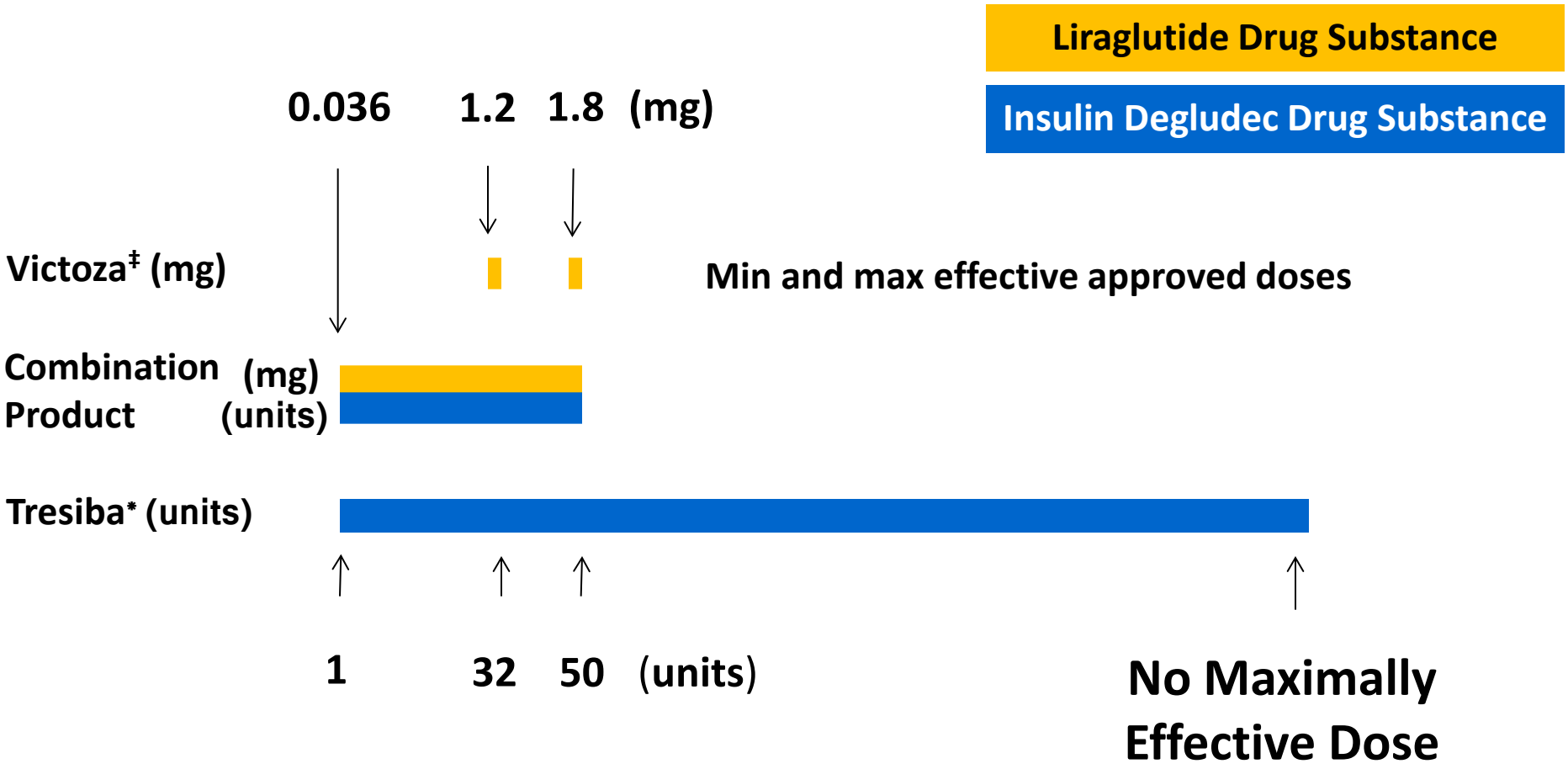
GLP-1 = glucagon like peptide-1

Patient Population for Concurrent Use

- Who is a candidate for concurrent use?
  - A. *All patients failing a first line agent?*
  - B. *Only a specific subpopulation of patients failing a first line agent?*
  - C. *Only patients inadequately controlled on oral agents and a regimen including either a GLP-1 receptor agonist or a basal insulin?*
  - D. *Only patients already using both?*
  - E. *All of the above*

- The applicant has studied the combination in
  - *Patients <u>not previously treated</u> with either an insulin or a GLP-1 receptor agonist who have failed a first line agent (i.e.,metformin)*
  - *Patients inadequately controlled on a basal insulin (i.e., GLP-1 add-on paradigm)*
  - *Patients inadequately controlled on a GLP-1 (i.e., insulin add-on paradigm)*

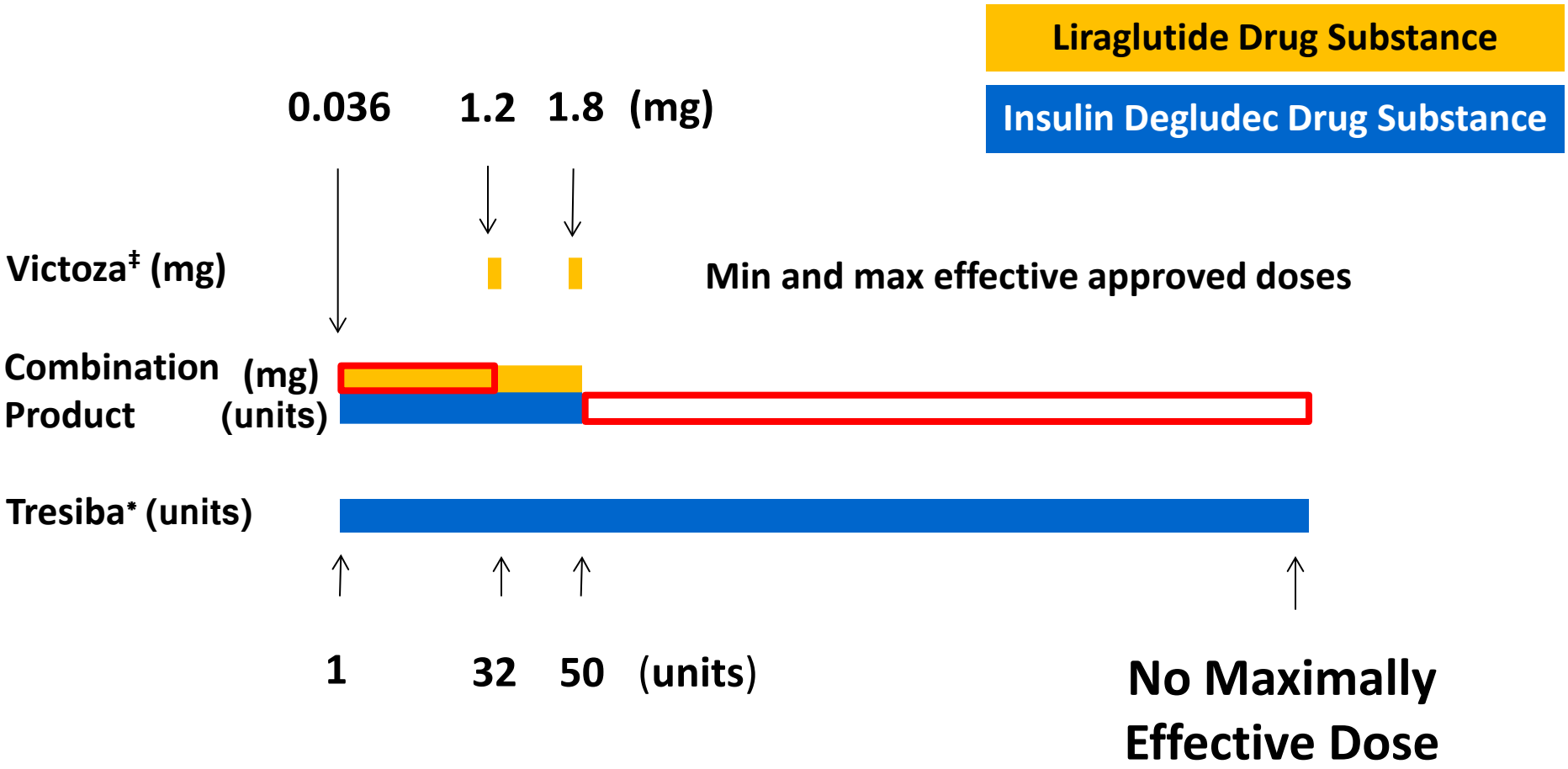
Proposed Dosage of Combination Product



‡Liraglutide drug product indicated for type 2 DM

*Degludec drug product indicated for type 2 DM

Proposed Dosage of Combination Product



‡Liraglutide drug product indicated for type 2 DM

*Degludec drug product indicated for type 2 DM

Charge to the Committee Discussion Points and Vote

Presentation Overview

- Background and product overview
- Phase 3 trial designs
- Statistical Efficacy – Anna Kettermann
- Clinical relevance
- Safety findings

Abbreviations

GLP-1	Glucagon-like peptide-1 receptor agonist
IDeg	Insulin degludec
IDegLira	Insulin degludec and liraglutide
IGlar	Insulin glargine

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Available Therapeutic Options for The Management of Diabetes

Pharmacologic Class	Approved Drug Products
ALPHA-GLUCOSIDASE INHIBITORS	acarbose; meglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP-4 INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Albiglutide; Dulaglutide; Exenatide; Exenatide LAR, **Liraglutide**
INSULINS AND INSULIN ANALOGUES	**Insulin Degludec**; Insulin Detemir; Insulin Glargine; Insulin Isophane;
MEGLITINIDES	Nateglinide; Repaglinide
SGLT2 INHIBITORS	Canagliflozin; Dapagliflozin; Empagliflozin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glyburide (Glibenclamide); Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone

Source: Product labeling, available at Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Available Therapeutic Options for The Management of Diabetes

Pharmacologic Class	Approved Drug Products
Alpha-Glucosidase Inhibitors	Acarbose; Meglitol
Amylin Mimetics	Pramlintide
Biguanides	Metformin
Bile Acid Sequestrants	Colesevelam
Dopamine-2 Agonists	Bromocriptine
DPP-4 Inhibitors	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 Receptor Agonists	Albiglutide; Dulaglutide; Exenatide; Exenatide LAR, **Liraglutide**
Insulins and Insulin Analogues	**Insulin Degludec**; Insulin Detemir; Insulin Glargine; Insulin Isophane;
Meglitinides	Nateglinide; Repaglinide
SGLT2 Inhibitors	Canagliflozin; Dapagliflozin; Empagliflozin
Sulfonylureas	Chlorpropamide; Glimepiride; Glipizide; Glyburide (Glibenclamide); Tolazamide; Tolbutamide
Thiazolidinediones	Pioglitazone; Rosiglitazone

Source: Product labeling, available at Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Insulin Degludec

- Approved in 2015 under the trade name Tresiba
- A long-acting insulin analog indicated to improve glycemic control in adults with diabetes mellitus
- Dosed once-daily at any time of day
- The dose of insulin degludec is individualized based on the patients metabolic needs, blood glucose monitoring results and glycemic goal

Liraglutide

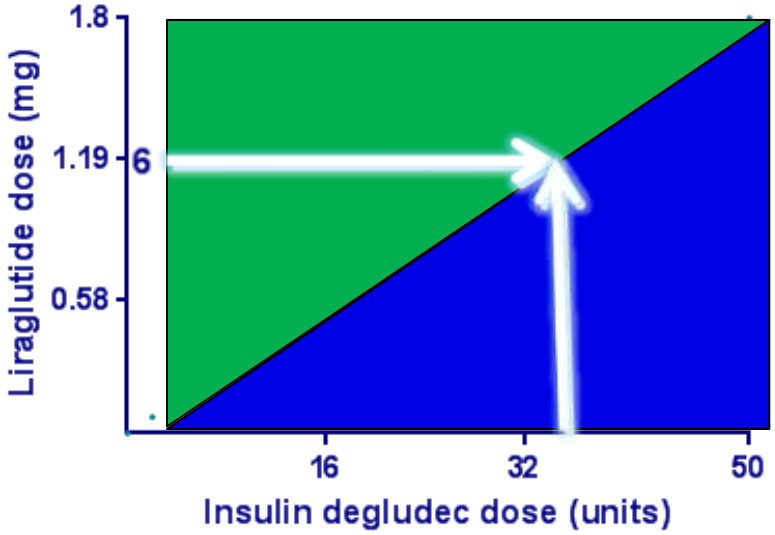
- Liraglutide was approved with the trade name Victoza in 2010 at a maximum dose of 1.8 mg as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

- Initiated at 0.6 mg per day for one week; after one week the dose should be increased to 1.2 mg
  - 0.6 mg is a starting dose to improve gastrointestinal tolerability and is not an approved dose to improve glycemic control

- If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to a maximum dose of 1.8 mg

IDegLira Dosing

- Fixed-ratio combination of degludec and liraglutide
  - Identical drug substances to individual marketed products
- For every **unit** of insulin degludec there is **0.036 mg** of liraglutide
- Titrated in increments of '1'
  - Maximum IDeg dose of 50 units and 1.8 mg of liraglutide



IDegLira Dosing

- Fixed ratio of components does not allow for individual dosing, as when used as separate products

- Clinical implication:
  - *Initiation of IDegLira in patients on maximal dose of Victoza*
    - At switch will require a reduction the liraglutide dose and add insulin
  - *Reduction of insulin dose due to hypoglycemia*
    - If on IDegLira and experience hypoglycemia would have to decrease dose of both products (not just insulin component)

Program Objectives: Combination drug

- Trials should demonstrate that each component of the combination drug has an effect on HbA1c to meet the regulation

> 21CFR 300.50 - where two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

Program Objectives
IDegLira Program

- No precedent to apply the combination rule to a product that combines a titratable drug with a fixed-dose drug
- Question of best trial design to demonstrate contribution of the fixed-dose liraglutide to the glycemic effect
- FDA agreed it would be acceptable to 'cap' the dose of IDeg to evaluate superiority of IDegLira vs. IDeg
- Would meet regulatory requirement
  - residual uncertainty about how this data would be generalizable to clinical practice

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Subjects Not Previously Treated with GLP-1 or Basal Insulin

All trials 26-week duration for primary endpoint

Trial 3697
Inadequately controlled on

met ± pio

Open-label

- **IDegLira +** met ± pio
- **Liraglutide +** met ± pio
- **IDeg uncapped+** met ± pio

Demographics (mean)

Age: 55 years

BMI: 31 kg/m^2

Diabetes duration: 7 years

HbA1c: 8.3%

Add on to OAD(s): met +/- pio

Clinical scenario: Subjects not previously treated with GLP-1 or insulin (start two drugs at once)

Met=metformin; pio=pioglitazone; OAD= oral antidiabetic drug

Subjects Not Previously Treated with GLP-1 or Basal Insulin

All trials 26-week duration for primary endpoint

Trial 3951
Inadequately controlled on

SU ± met

Double-blind

- **IDegLira +** SU ± met
- **Placebo +** SU ± met

Demographics (mean)

Age: 60 years
BMI: 32 kg/m^2
Diabetes duration: 9 years
HbA1c: 7.9 %
Add on to OAD(s): SU +/- met

Clinical scenario: Subjects not previously treated with GLP-1 or insulin (start two drugs at once)

Met=metformin; SU=sulfonylurea; OAD= oral antidiabetic drug

Previous Insulin Users
(20-40 units/day)

All trials 26-week duration for primary endpoint

Trial 3912
Inadequately controlled on:

Basal insulin **20-40 units** + met ± SU ± glinide

- **IDegLira** + met
- **IDeg Cap 50 units** + met

Double-blind

Demographics (mean)

Age: 57 years
BMI: 34 kg/m^2
Diabetes duration: 11 years
HbA1c: 8.8%
Add on to OAD(s): met
Insulin dose: 29 units

Clinical scenario: Sequential add-on in patients failing basal insulin

Met=metformin; OAD= oral antidiabetic drug

Previous Insulin Users
(20-50 units of glargine/day)

All trials 26-week duration for primary endpoint

Trial 3952
Inadequately controlled on:

20-50 units Insulin glargine + met

Open-label

- **IDegLira** + met
- **Insulin glargine uncapped** + met

Demographics

Age: 59 years
BMI: 32 kg/m^2
Diabetes duration: 12 years
HbA1c: 8.3%
Add on to OAD(s): met
Insulin dose: 32 units

Clinical scenario: Sequential add-on in patients failing basal insulin

Met=metformin; OAD= oral antidiabetic drug

Previous GLP-1 Analog Users (maximally dosed)

All trials 26-week duration for primary endpoint

Trial 3851

Inadequately controlled on:

Liraglutide QD or exenatide BID + met ± pio ± SU

Open-label

- **IDegLira** + met ± pio ± SU
- **Liraglutide QD or exenatide BID** + met ± pio ± SU

Demographics

Age: 58 years

BMI: 33 kg/m^2

Diabetes duration: 10 years

HbA1c: 7.8%

Add on to OAD(s): met ± pio ± SU

Clinical scenario: Sequential add-on in patients failing GLP-1

BID=twice daily; Met=metformin; pio= pioglitazone; SU=sulfonylurea; OAD=oral antidiabetic drug

Important Clinical Uses Not Studied

- There are potential clinically important uses of IDegLira that were not studied
- Comparing the effectiveness of IDegLira vs. independent injection of degludec and liraglutide 1.8 mg
  - May help inform selection of specific therapy
- Converting subjects using a long-acting GLP-1 and a basal insulin independently to IDegLira
  - Testing whether IDegLira is an option for patients already using both therapies

Dosing of IDegLira and Insulin Comparator

- Adjustments of IDegLira and comparator insulin or placebo should have been performed **twice weekly**, based on fasting SMPG goals.

SMPG (MG/DL)	DOSE CHANGE
Below goal	-2
At goal	0
Above goal	+2

Because titration occurred twice weekly, the most a dose could increase in a given week was 4 of IDegLira or 4 units of basal insulin

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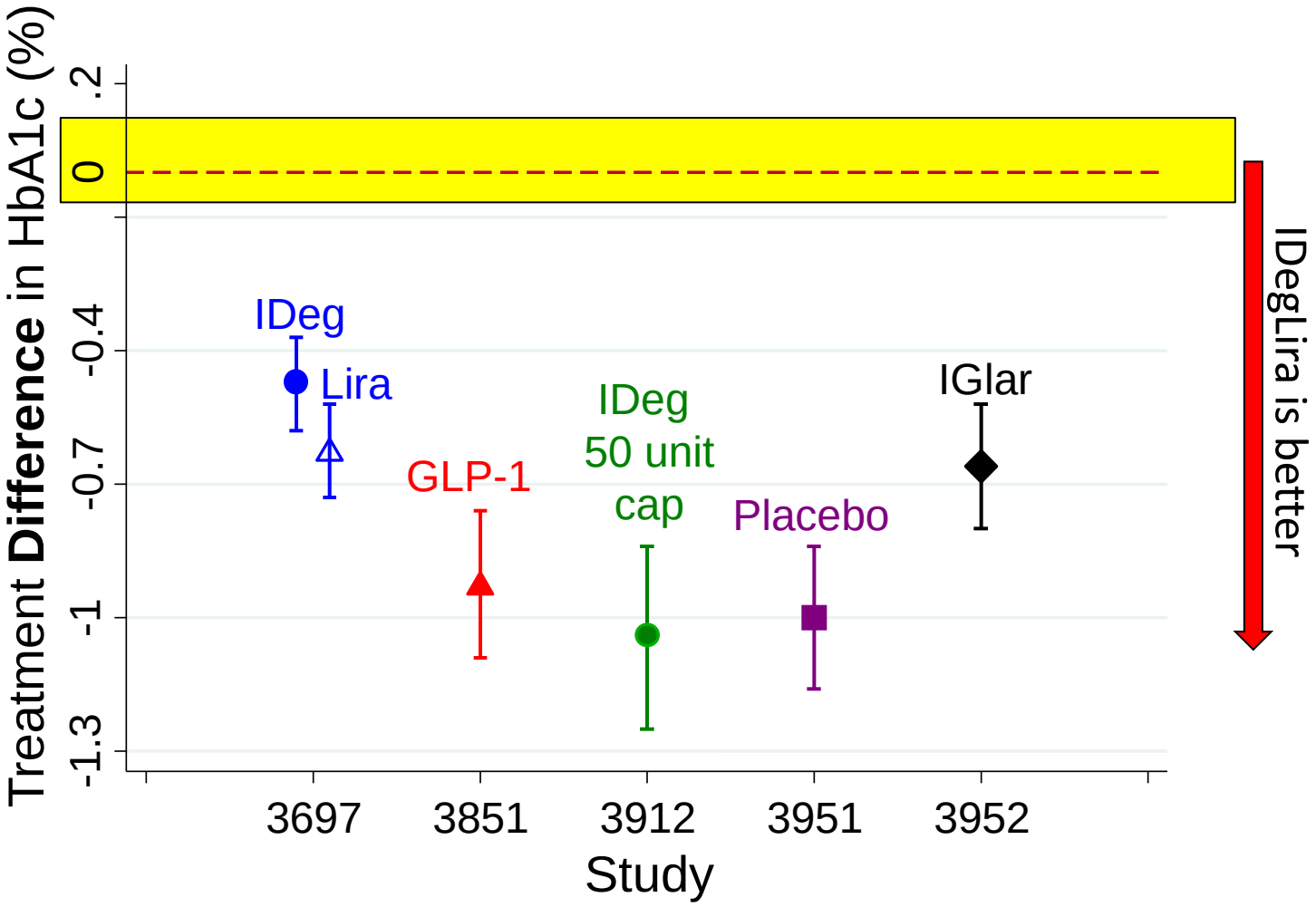
Statistical Assessment of Efficacy

- Trial objectives and primary efficacy results
- Secondary efficacy results
- Missing data
- Limitations of trial design and impact on interpretation of study outcome
  - External validity
- Conclusions

Objectives of IDegLira Phase 3 Program

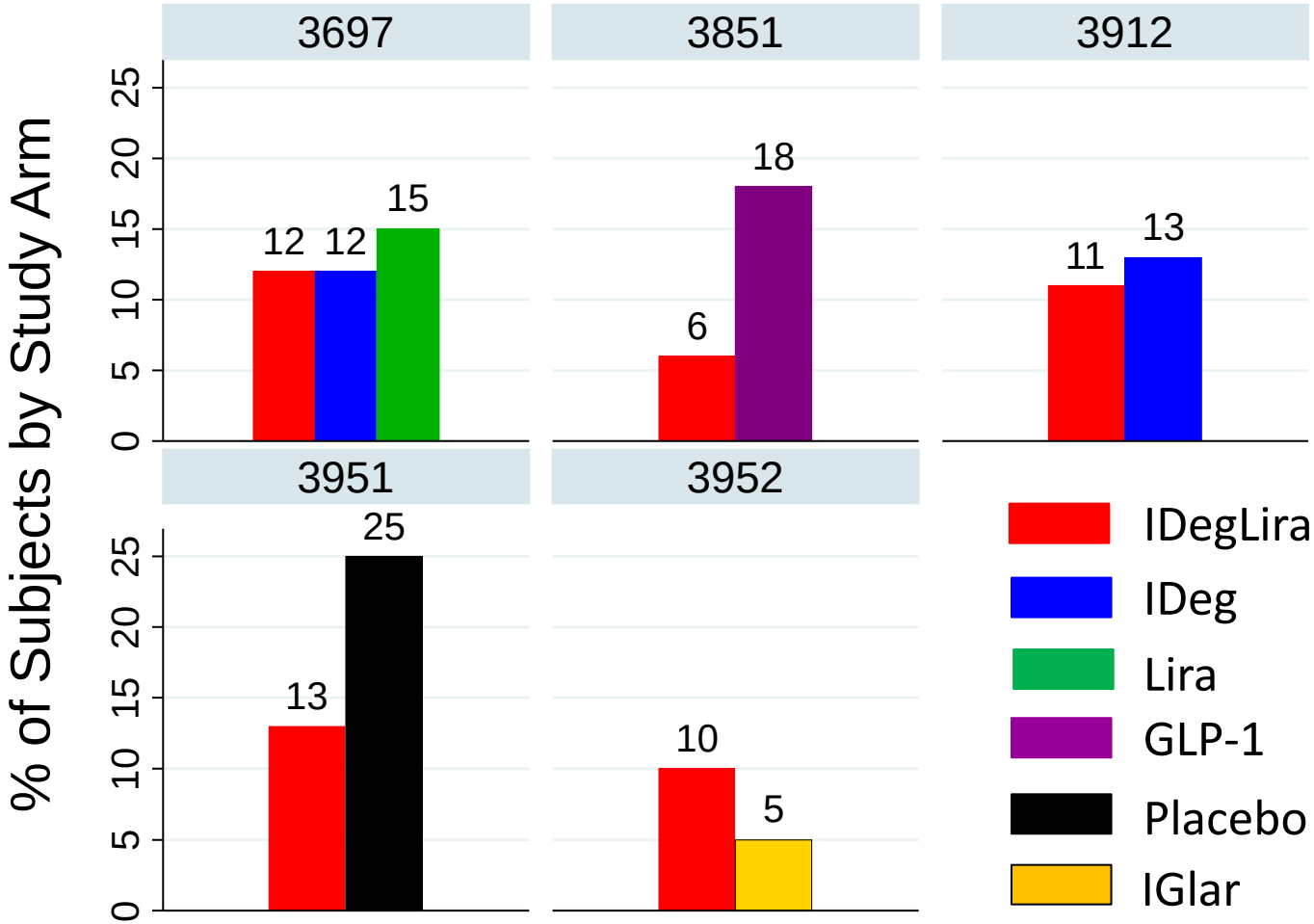
- Primary
  - Change in HbA1c from baseline to week 26
    - Superiority of IDegLira to comparator
- Analysis:
  - Mixed-Effect Model Repeated Measure (MMRM) approach
- Evaluation of impact of missing data:
  - Multiple Imputations and Tipping Point analyses

Primary Analysis Results (MMRM)



Missing Data

Subjects Who Did Not Complete 26-week Study



Limitations of data collection: subjects who dropped out were not followed after the time of dropout (no retrieved dropout)

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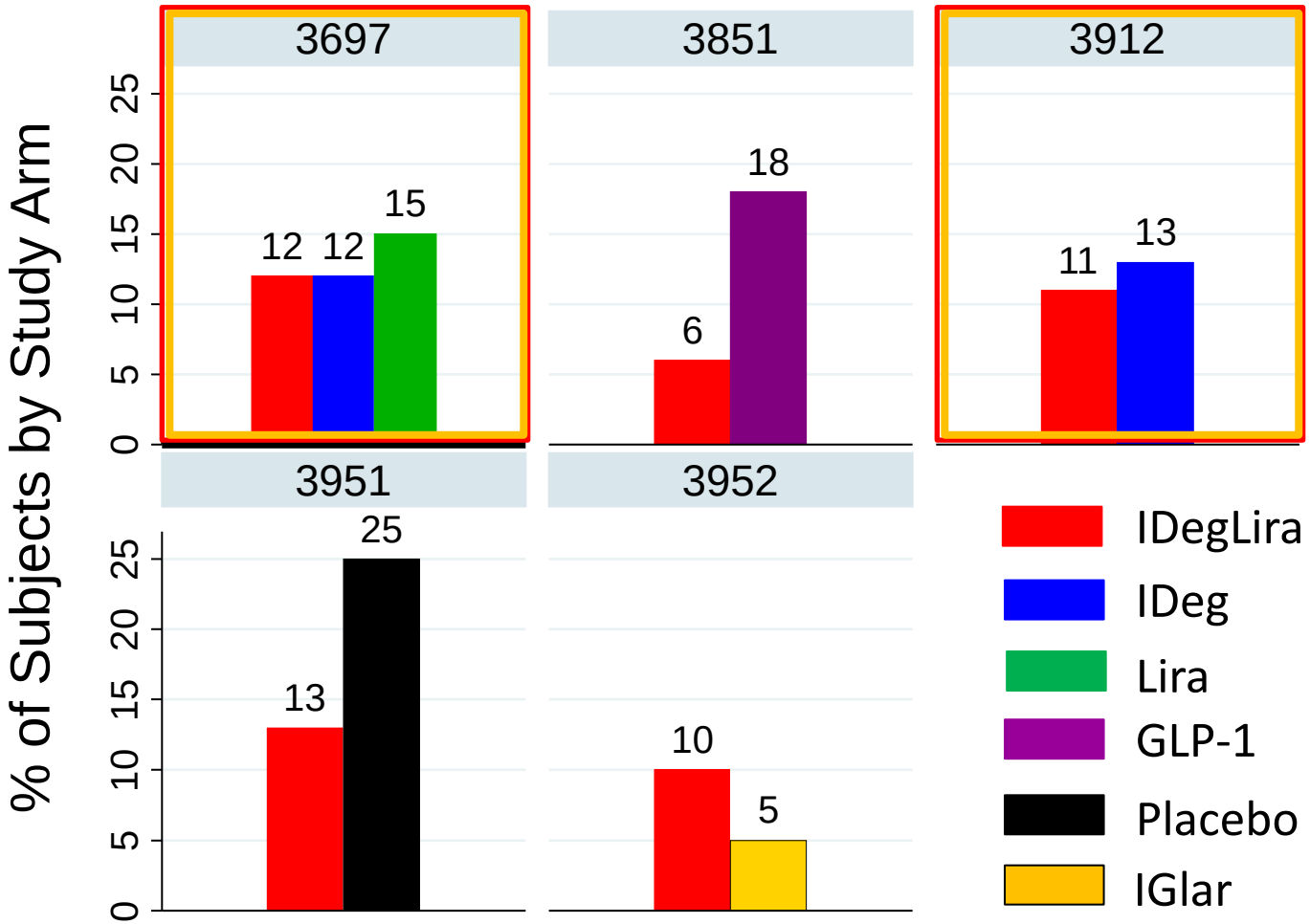

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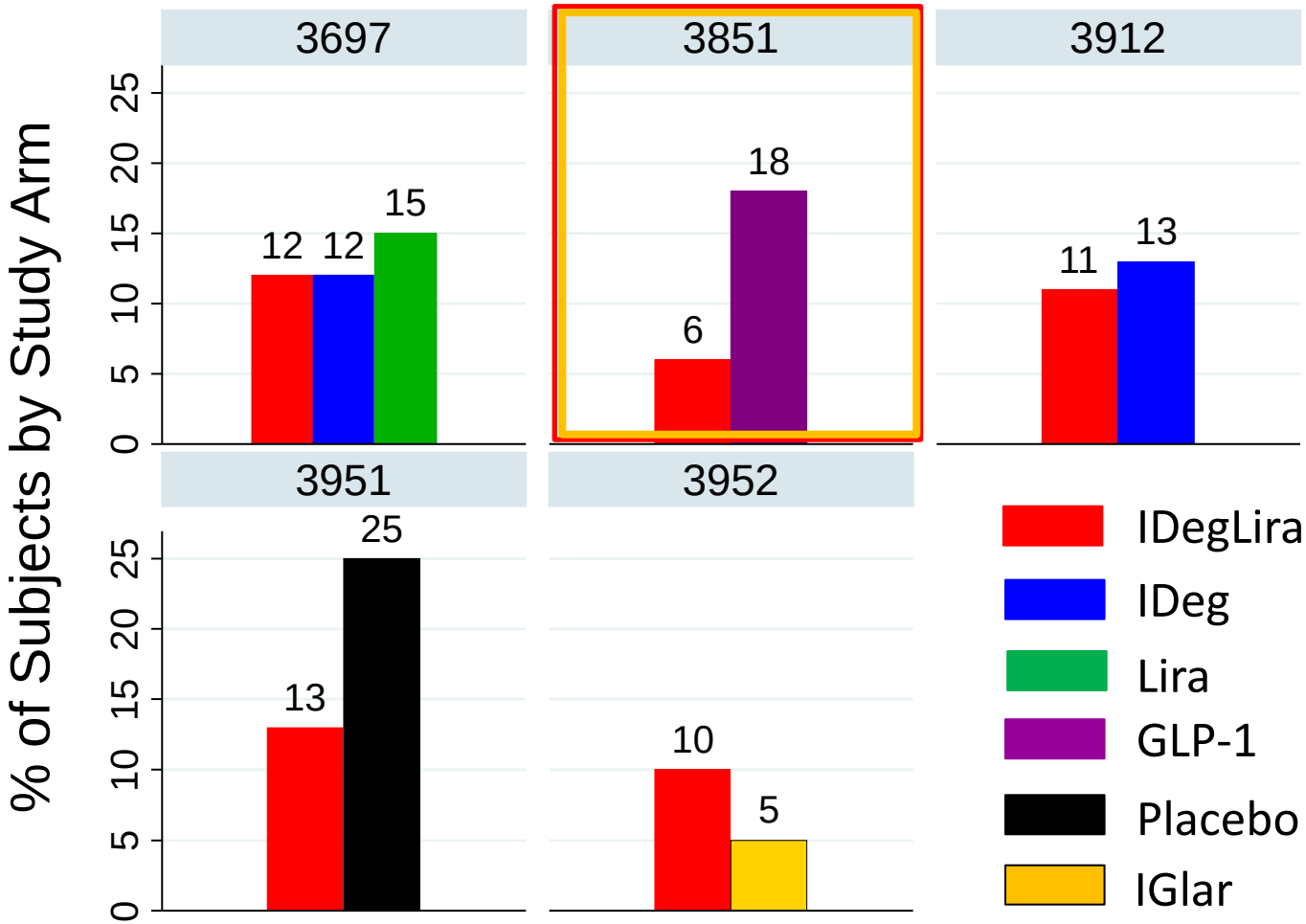

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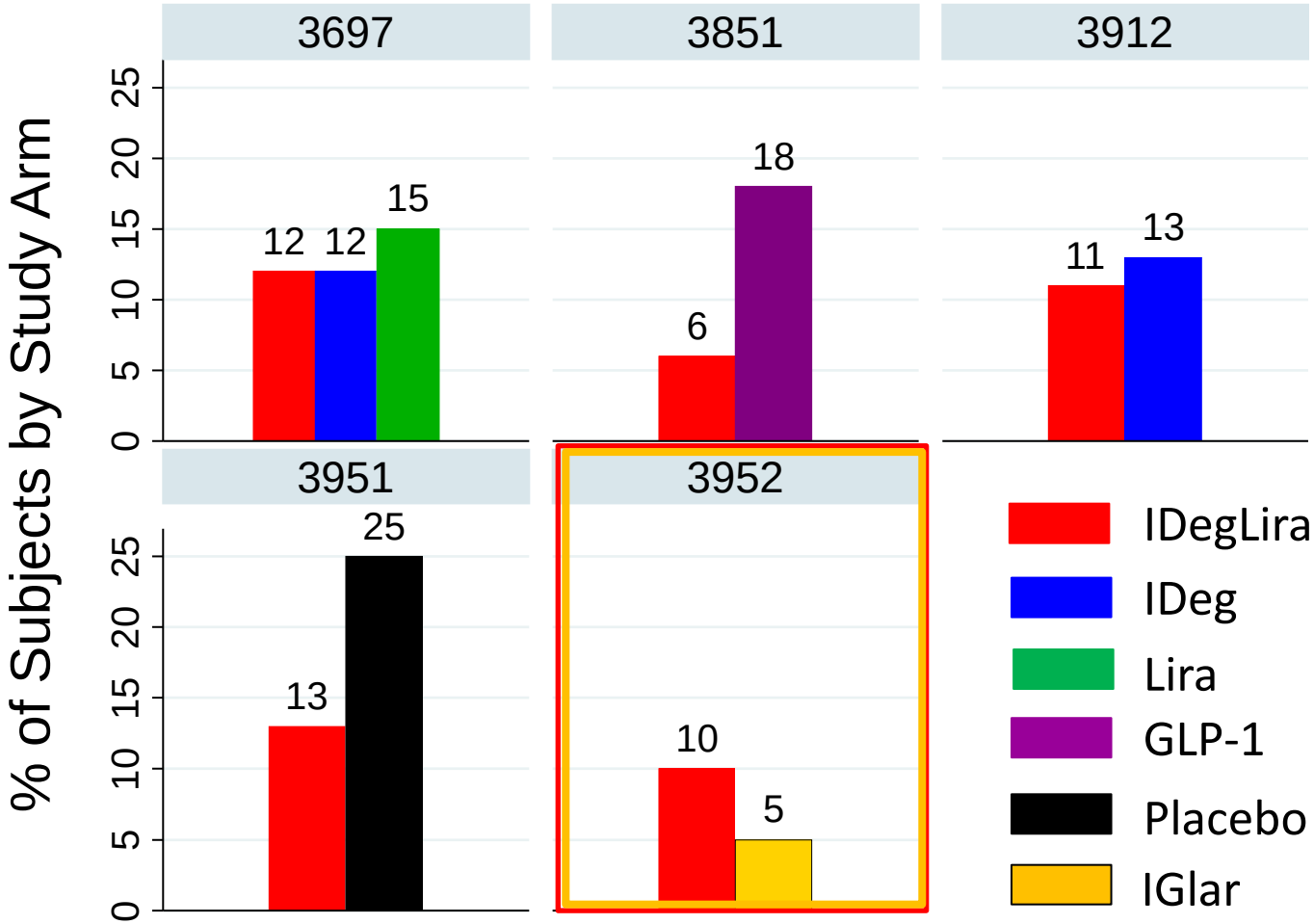

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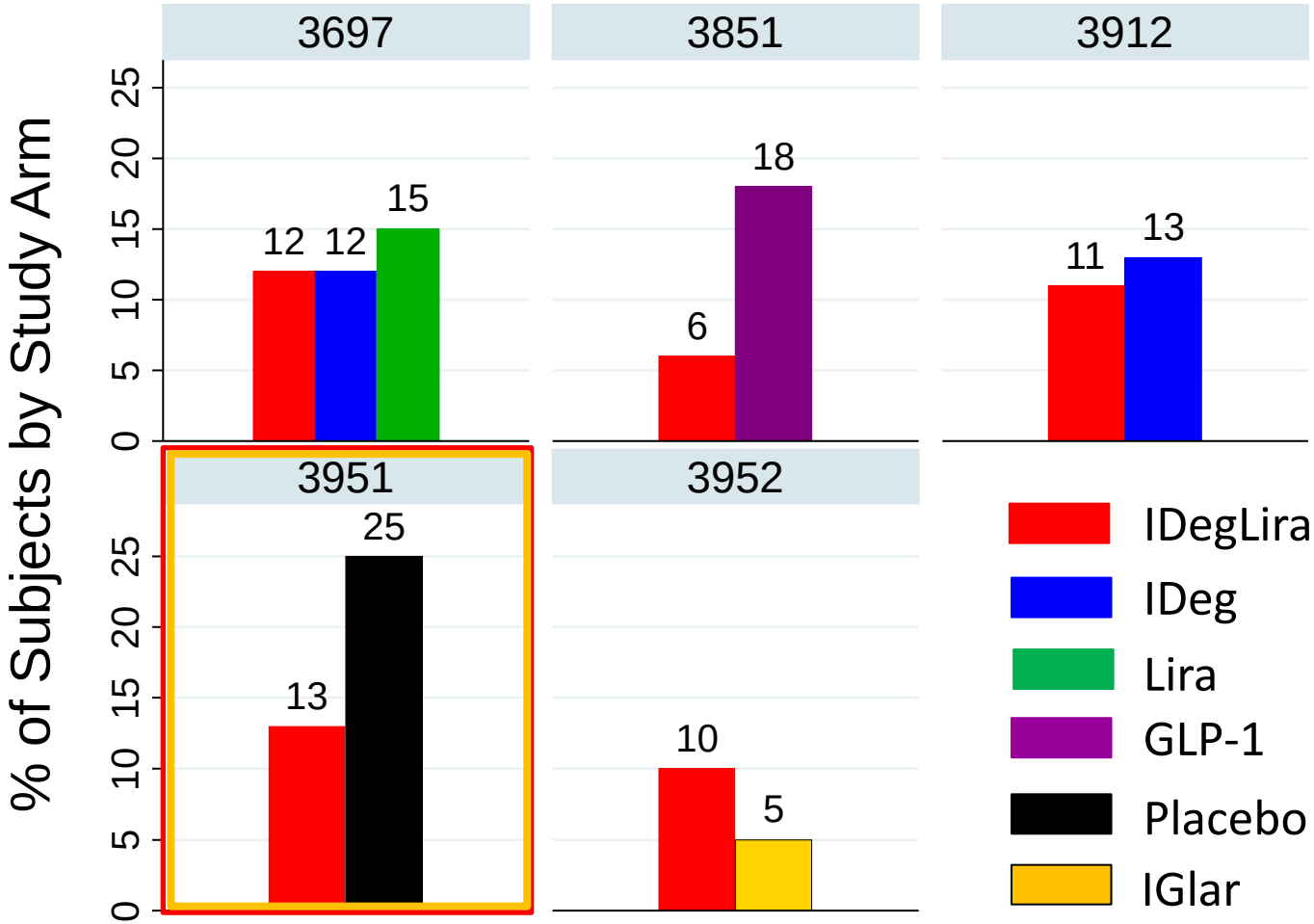


Limitations of data collection: subjects who dropped out were not followed after the time of dropout (no retrieved dropout)

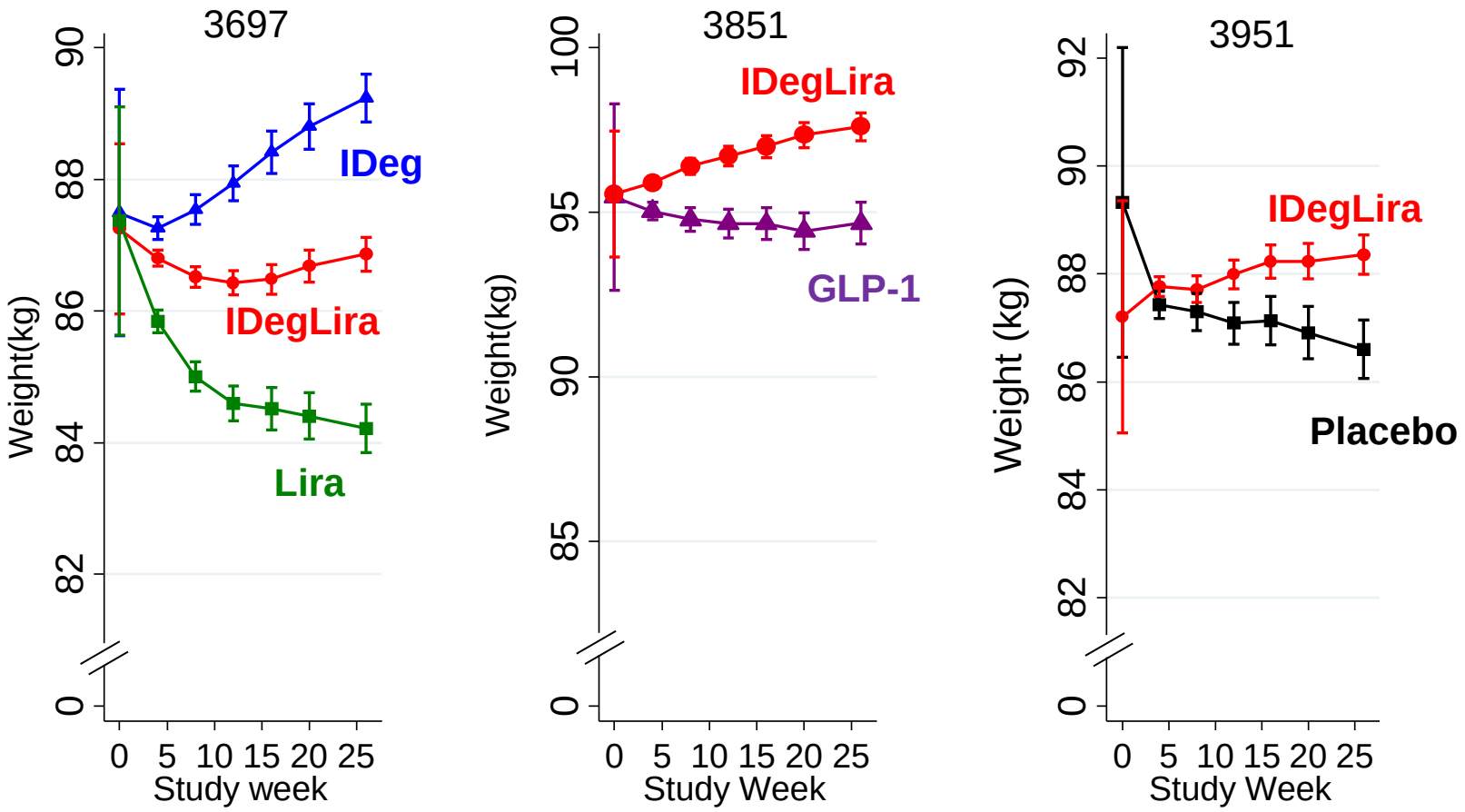
Missing Data

- Sensitivity analyses
  - Results of Multiple Imputations (MI)
    - Jump to Reference and Copy to Reference approaches produced similar results
    - All estimates and 95% intervals of the difference between IDegLira and comparators were in favor of IDegLira
  - Results for tipping point analysis (TP)
    - It would take impractical circumstances to tip the results from a conclusion of superiority to failing to conclude superiority

Objectives of IDegLira Phase 3 Program

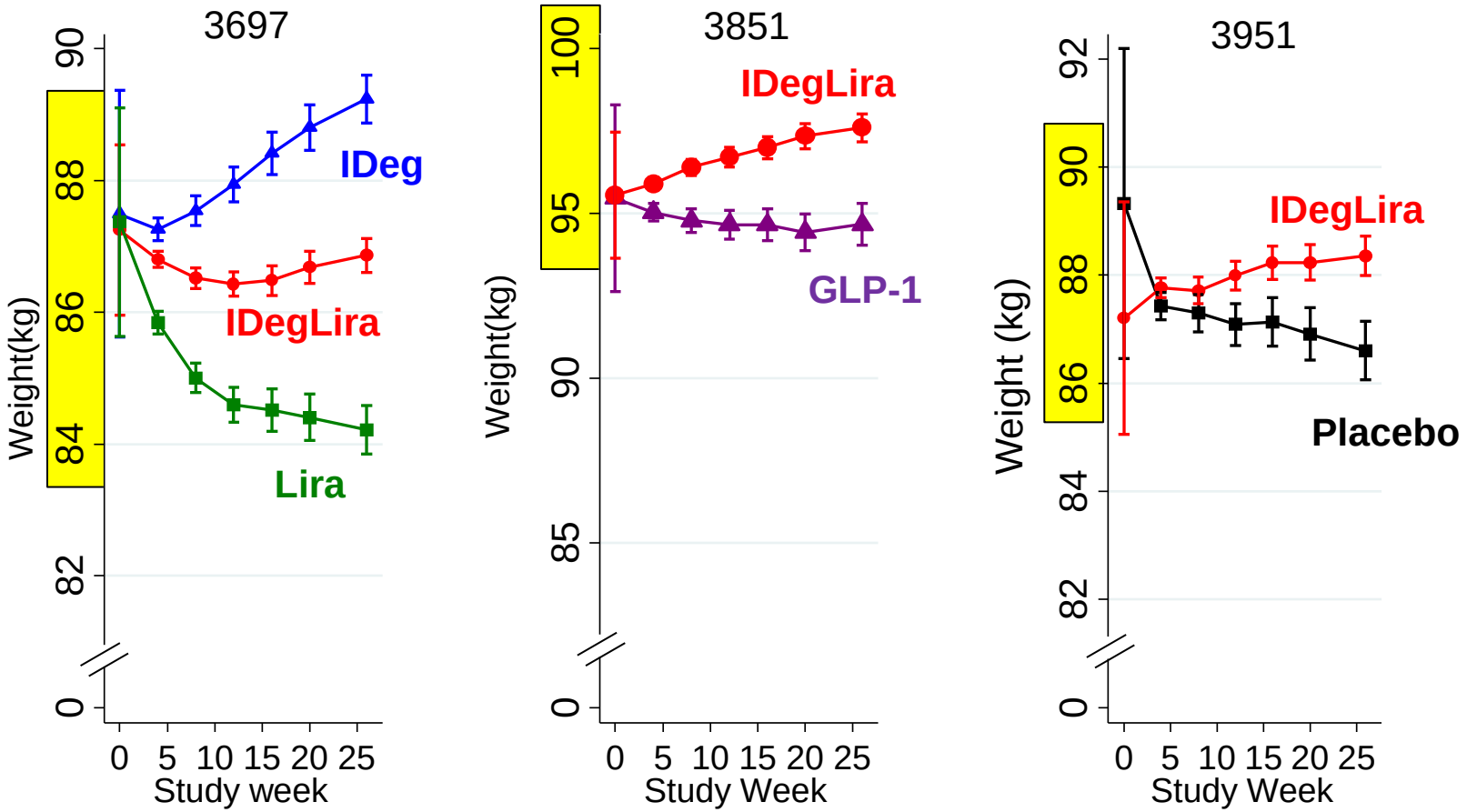
- Secondary
  - Change in body weight
  - Number of treatment emergent confirmed hypoglycemia cases
    - Will be discussed as a safety endpoint

Secondary Endpoints: Longitudinal Changes in Body Weight*



*Results from MMRM analysis

Secondary Endpoints: Longitudinal Changes in Body Weight*

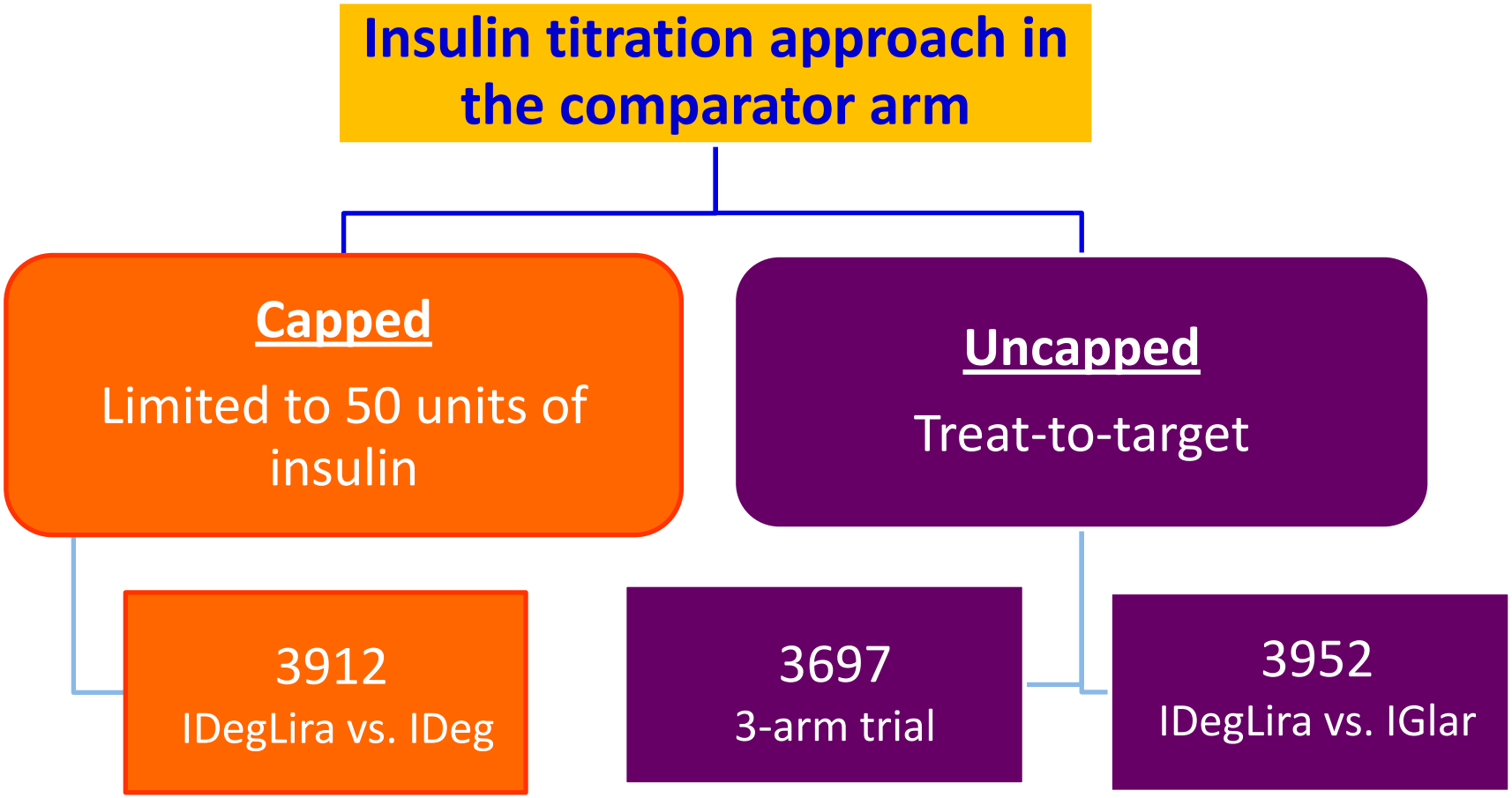


*Results from MMRM analysis

Limitation of Body Weight Data – Statistical Perspective

- Short duration of follow-up
  - Only one study with 52 week data
  - No retrieved dropout, i.e. no follow-up for subjects who discontinued study prematurely
- Change in body weight was not consistent across all trials
  - Most likely due to differences in patient population and comparators

Limitations of Trial Design: Insulin Titration Approaches



Definition of Dose Stabilization

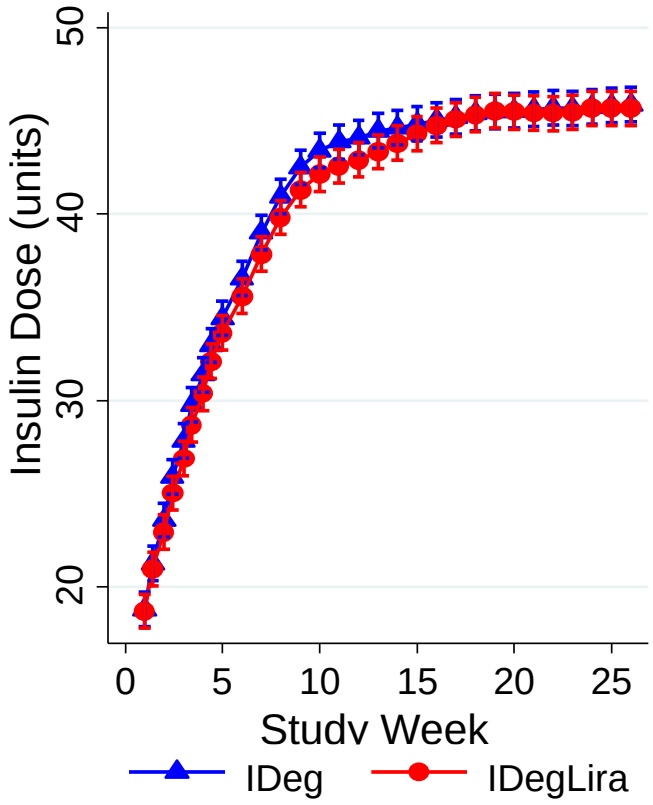
- Dose is considered to be **stable** when the investigator stopped increasing the dose
- **Time to dose stabilization** is time to when the dose increase had stopped
- Dose change is based on Self-Measured Plasma Glucose (SMPG) level
- MMRM, adjusted for covariates including baseline HbA1c.

Trial design: Dose Stabilization

Study 3912

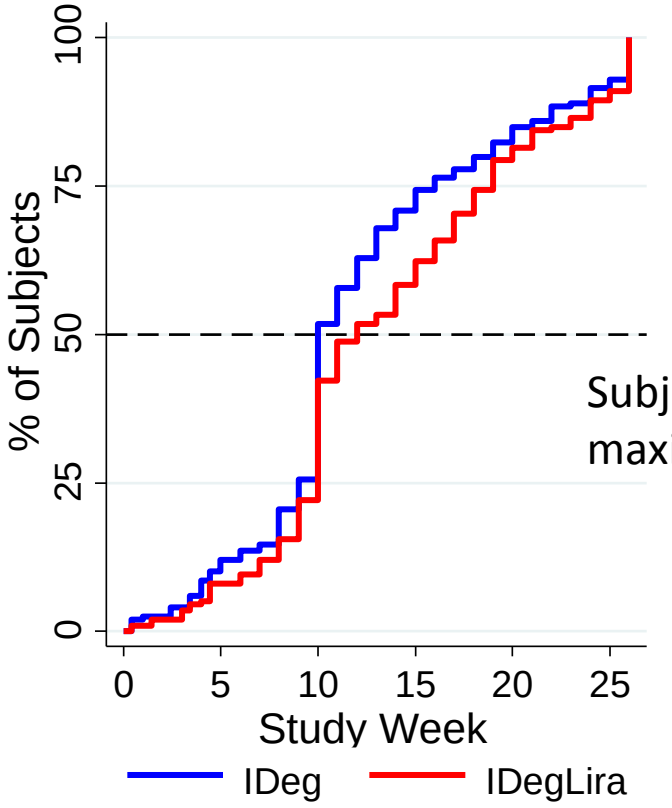
Capped

Insulin Dose by Week*



*Results from MMRM analysis

Time to Dose Stabilization§



§Kaplan-Meier curve

Subjects who reached maximum insulin dose:

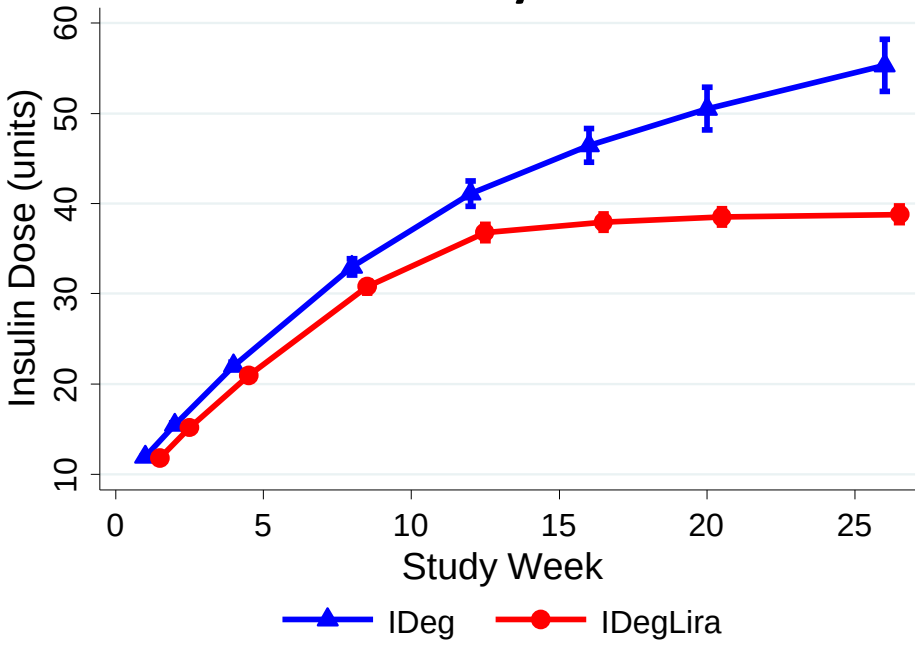
IDegLira	67.9%
IDeg	70.9%

Trial Design: Dose Stabilization

Study 3697

Uncapped

Insulin Dose by Week*



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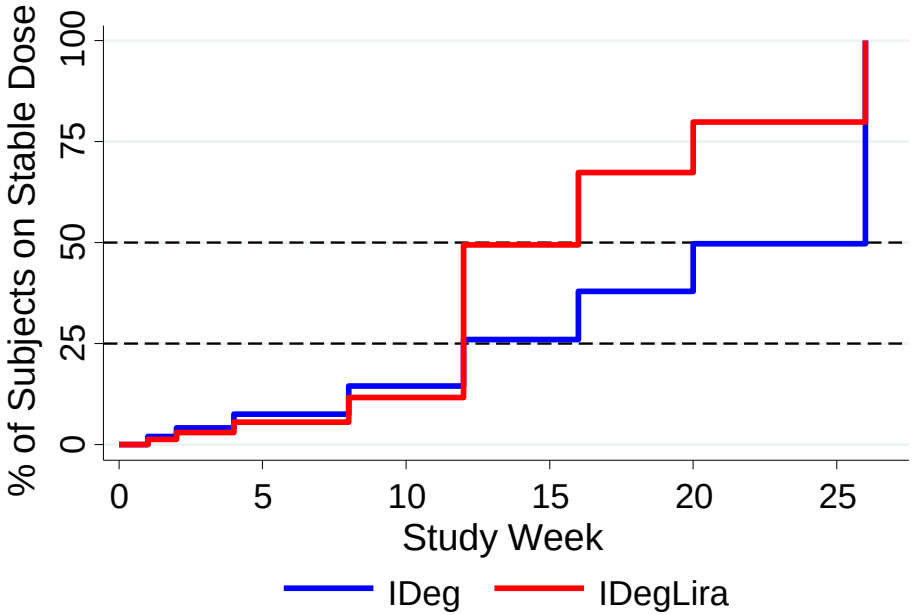

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Trial Design: Dose Stabilization

Study 3697

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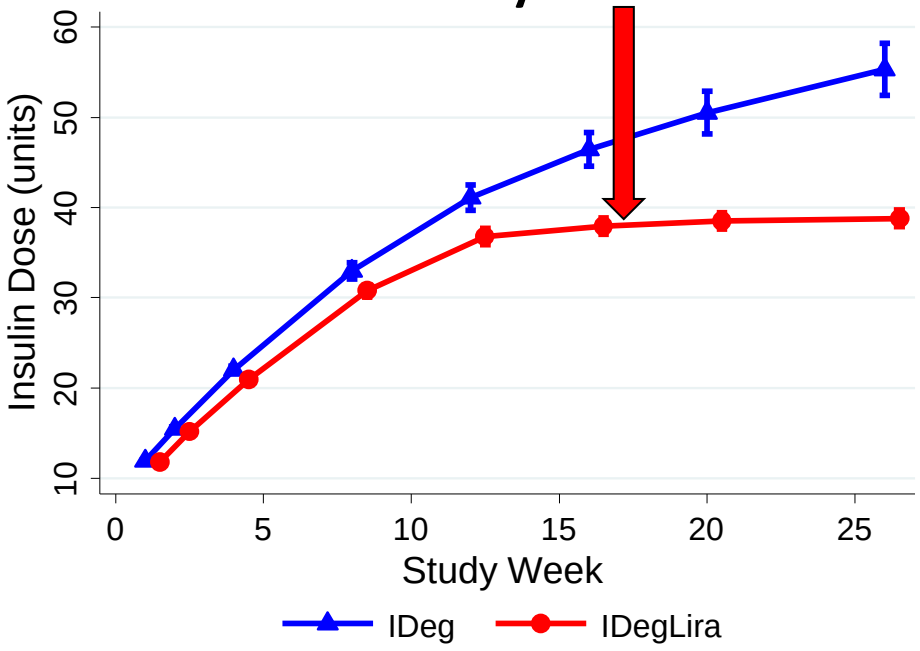

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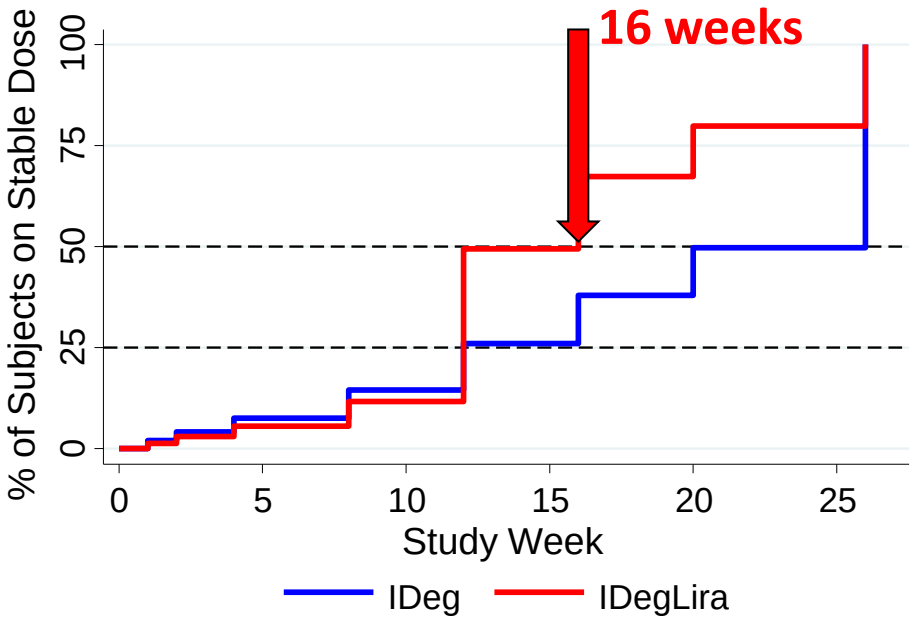

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Trial Design: Dose Stabilization

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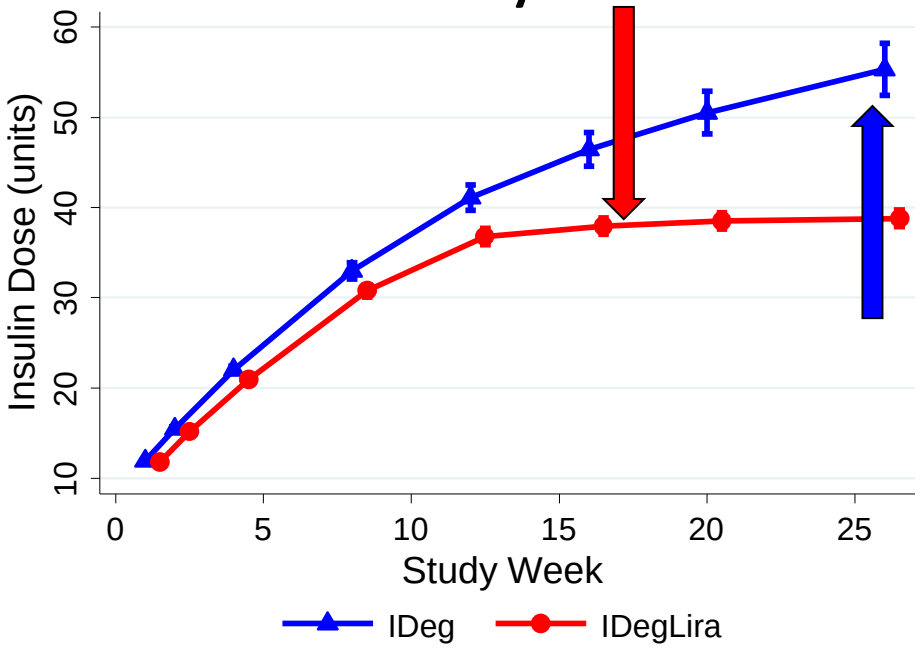

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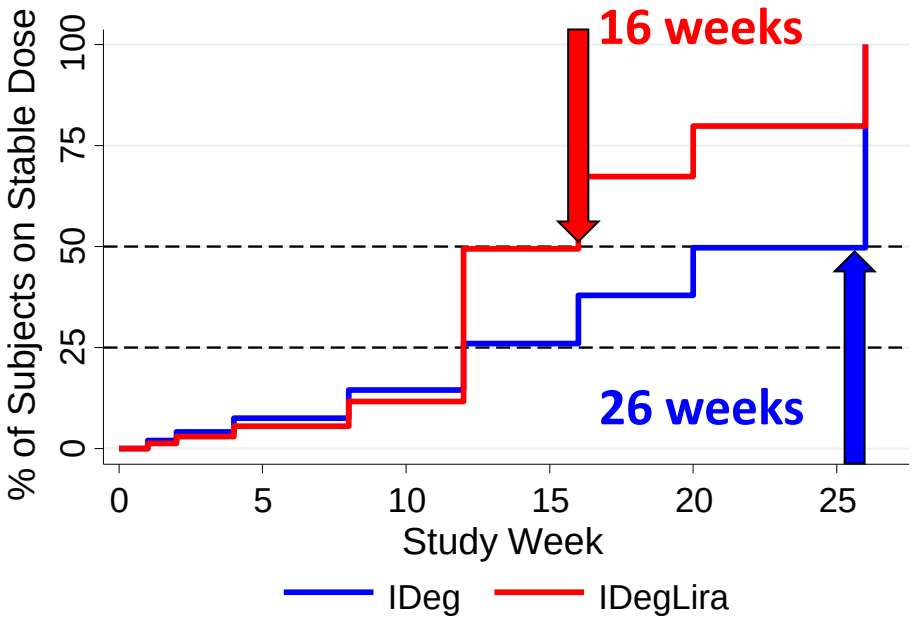

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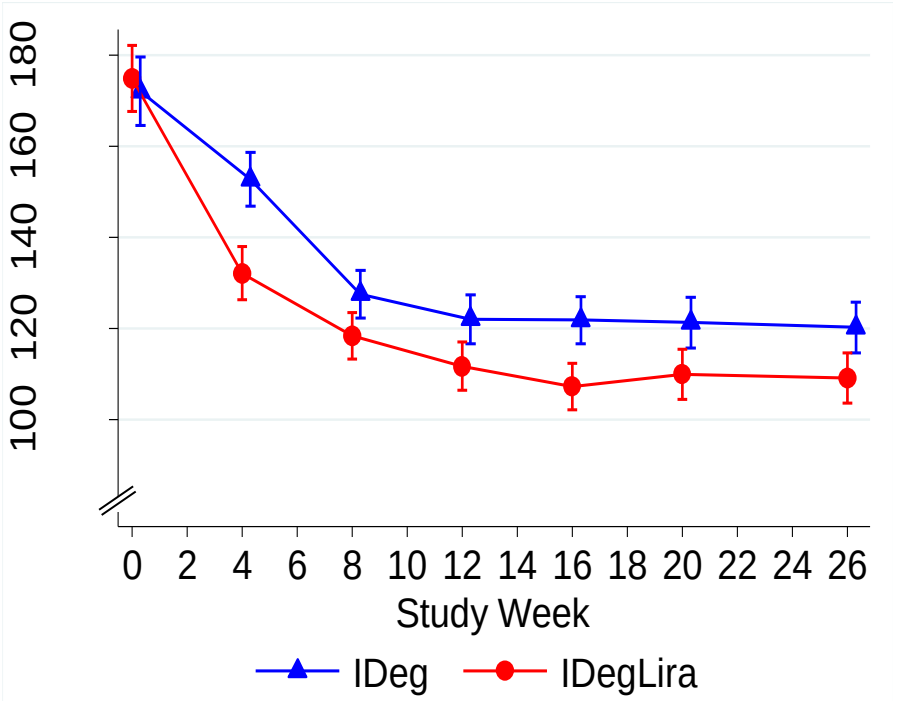
§Kaplan-Meier curve

FPG by Study Week

Study 3912

Fasting Plasma Glucose by Study Week*



Study 3697

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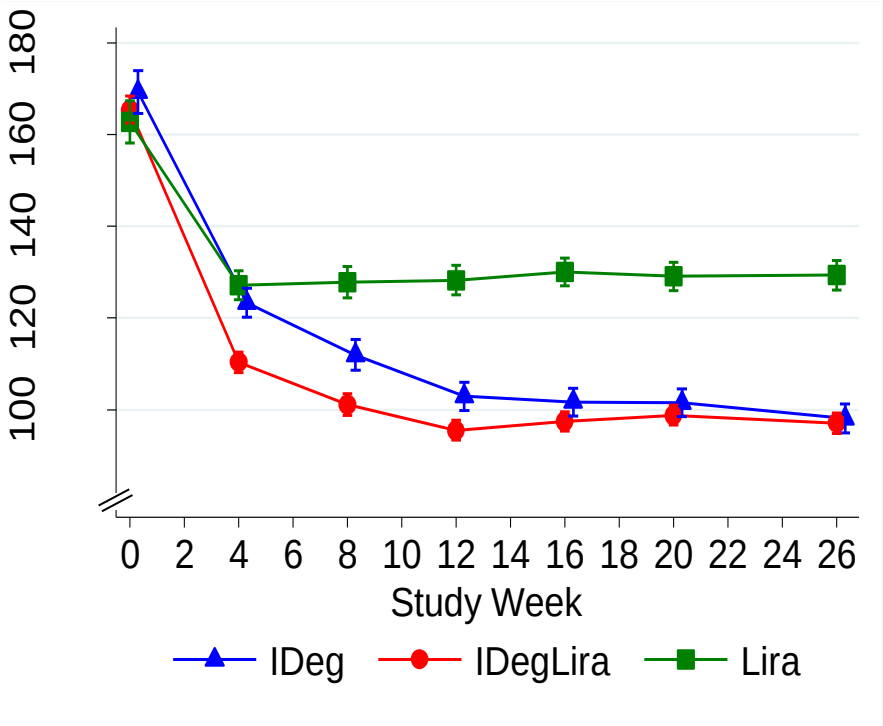

*Results from MMRM analysis

Conclusions

- Primary endpoint was met for all 5 trials
- Missing data did not impact the conclusion of superiority of IDegLira at week 26 on HbA1c change
- Concern that insulin titration resulted in overstating the treatment effect on HbA1c in insulin comparator trials
- Body weight changes were statistically different between arms
  - Although subjects on IDegLira had less weight gain than subjects on insulin, weight change among subjects on IDegLira was significantly smaller than weight reduction among subjects on GLP-1 and subjects on placebo

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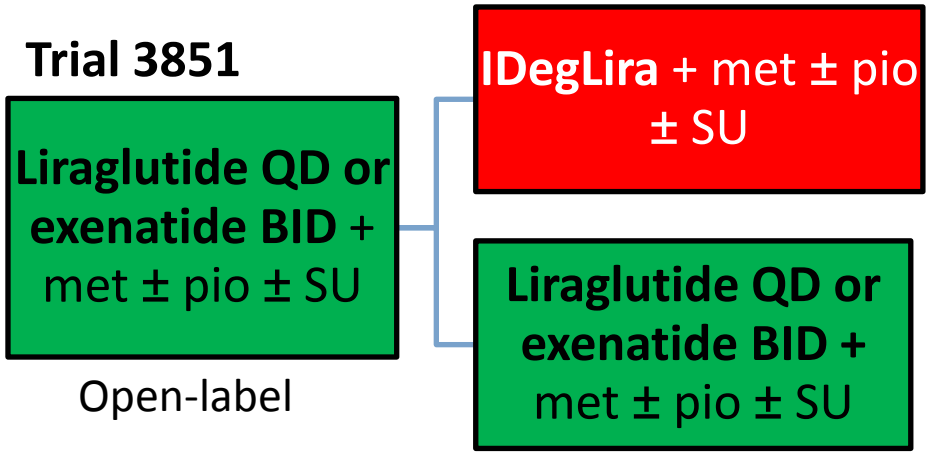
Interpretation of the Efficacy Results Non Insulin Comparators

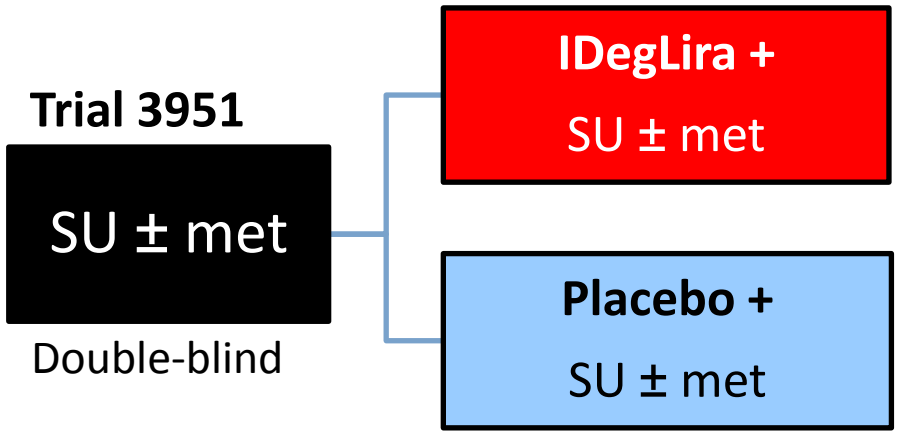
- IDegLira superior to continuation of GLP-1



Clinical scenario: Sequential add-on in patients failing GLP-1

Interpretation of the Efficacy Results Non Insulin Comparators

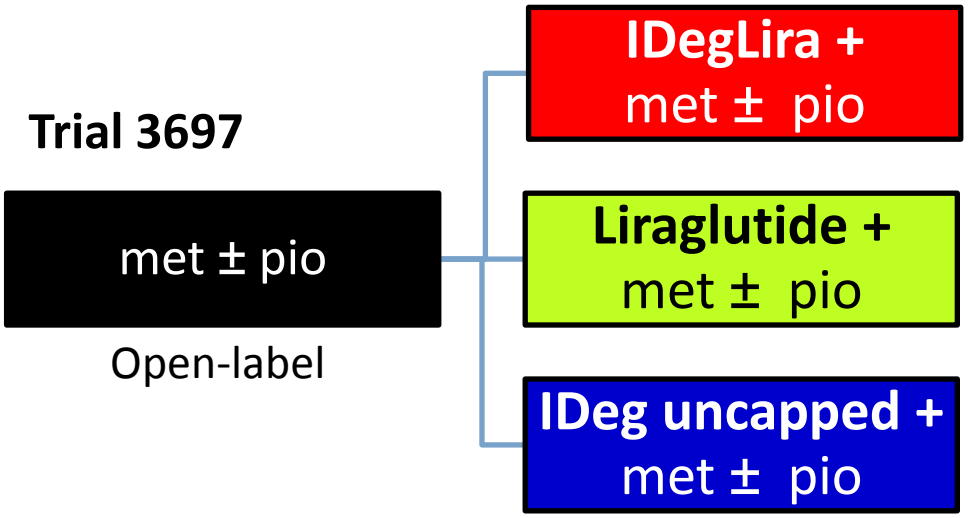
- IDegLira superior to placebo



Clinical scenario: Subjects not previously treated with GLP-1 or insulin (start two drugs at once)

Interpretation of the Efficacy Results Non Insulin Comparators

- IDegLira superior to liraglutide

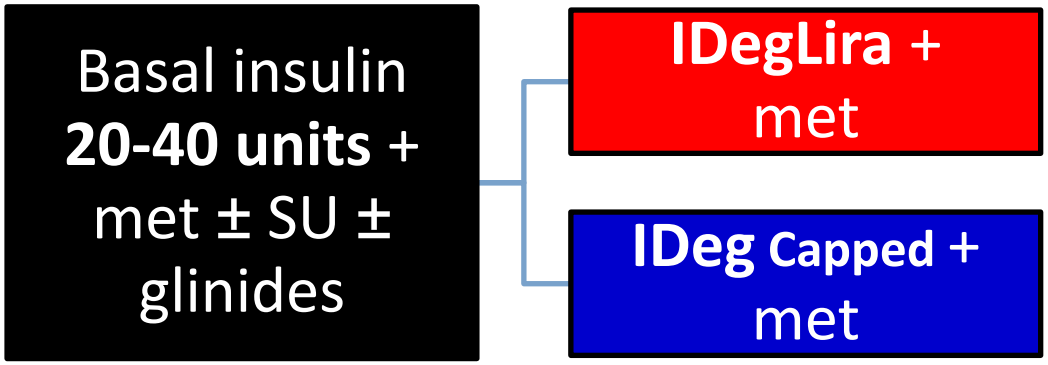


Clinical scenario: Subjects not previously treated with GLP-1 or insulin (start two drugs at once)

Interpretation of the Efficacy Results Insulin Comparator

- IDegLira superior to IDeg capped at 50 units, demonstrating contribution to glycemic control from liraglutide

Trial 3912
Double-blind

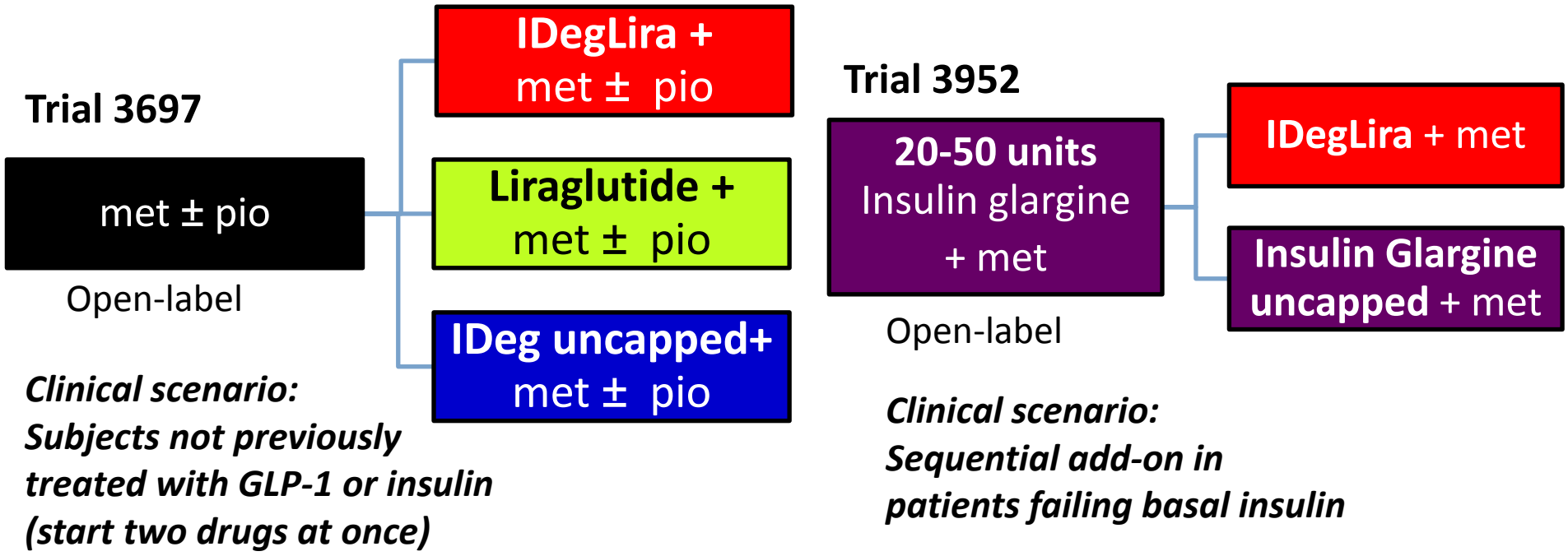


Clinical scenario: Sequential add-on in patients failing basal insulin

- Dosing limits generalizability to clinical practice

Interpretation of the Efficacy Results
Insulin Comparator

- IDegLira was superior to **uncapped** insulin

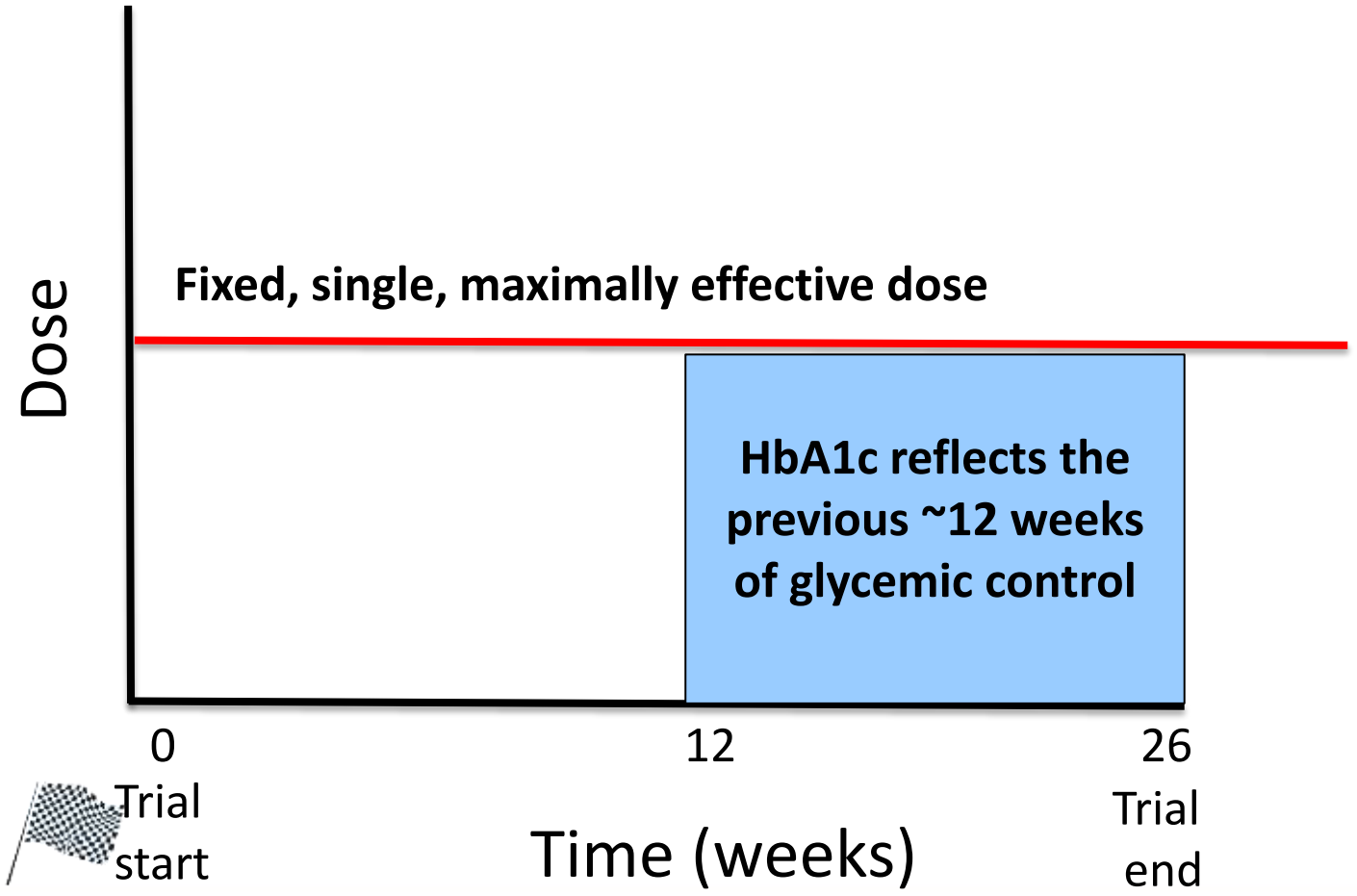


- Unclear external validity because of trial design and dosing issues

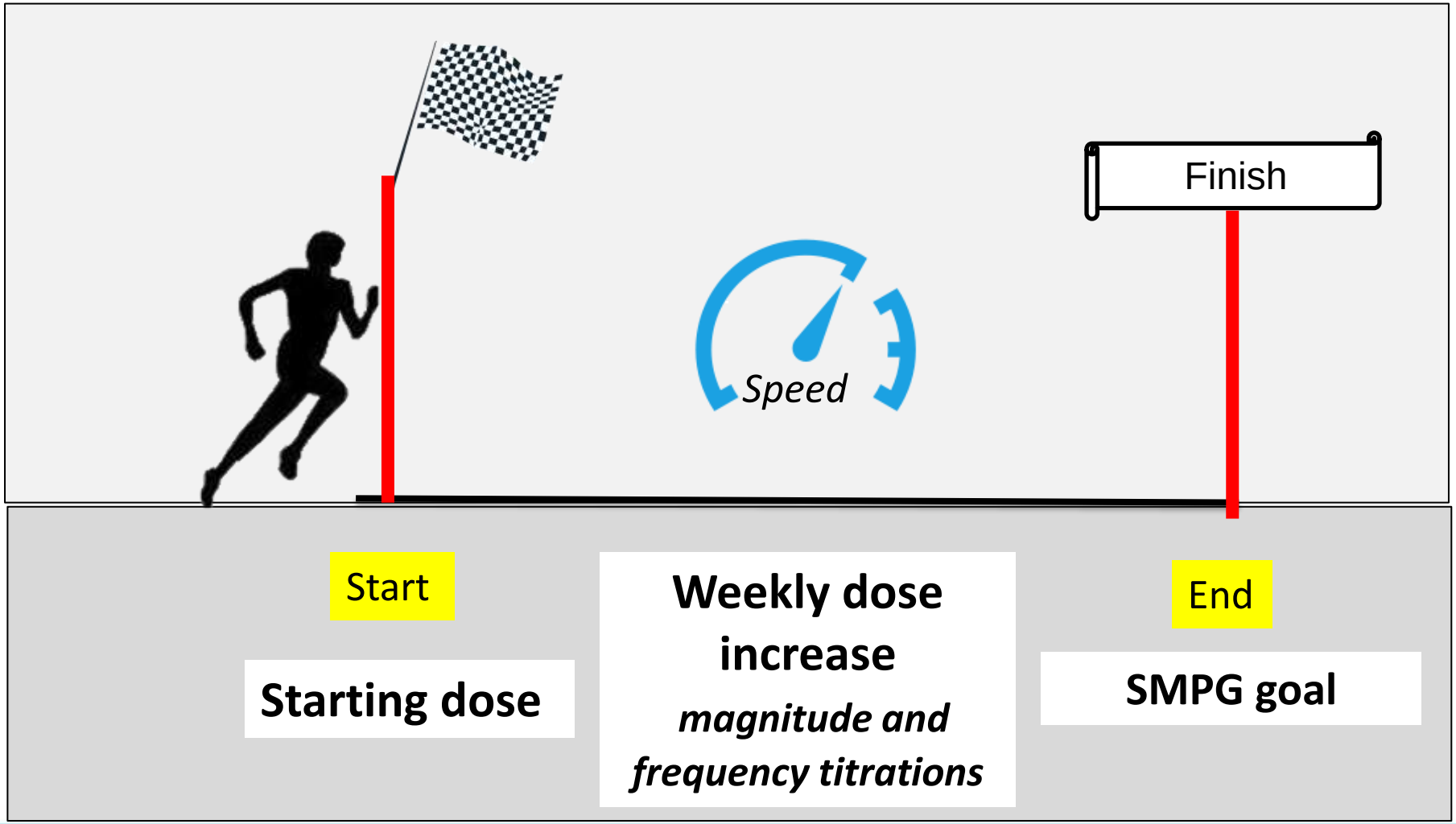
HbA1c Measurement

- HbA1c measures a time-weighted average of glucose concentrations over a period of 12-16 weeks in an individual subject
- Therefore, it would take 12 -16 weeks for a maximal drug effect to be fully reflected in the HbA1c measurement
- To fairly interpret the effect of a drug on HbA1c the maximally effective dose of a drug has to be reached at least 12-16 weeks before the final HbA1c measurement
- For fixed dose drugs this is not an issue, but for titratable drugs there can be challenges, as I will discuss in the next few slides

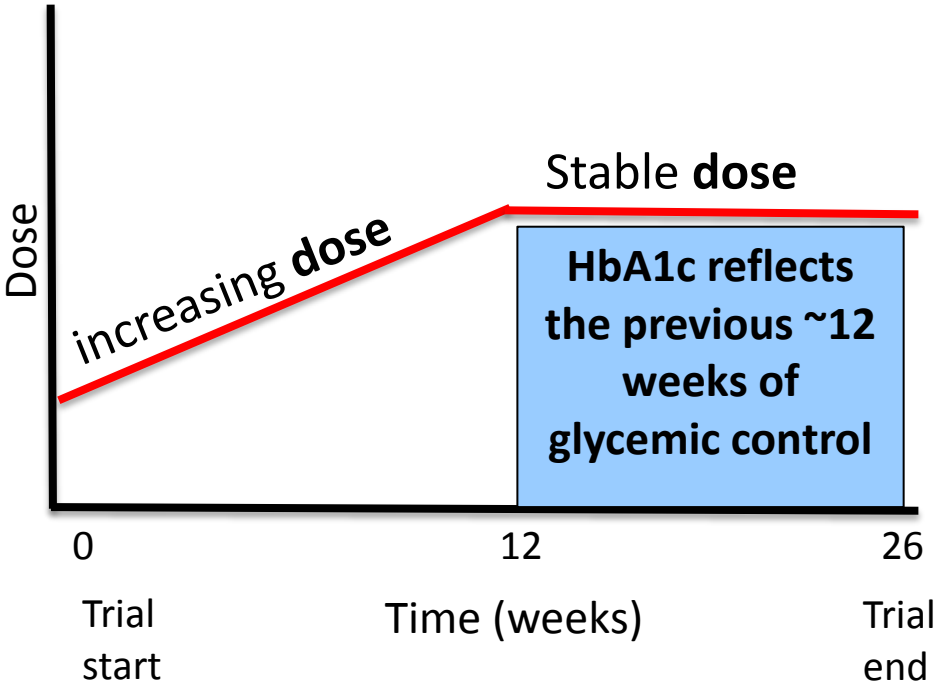
Interpretation of Change in HbA1c
Fixed-single-dose Drug



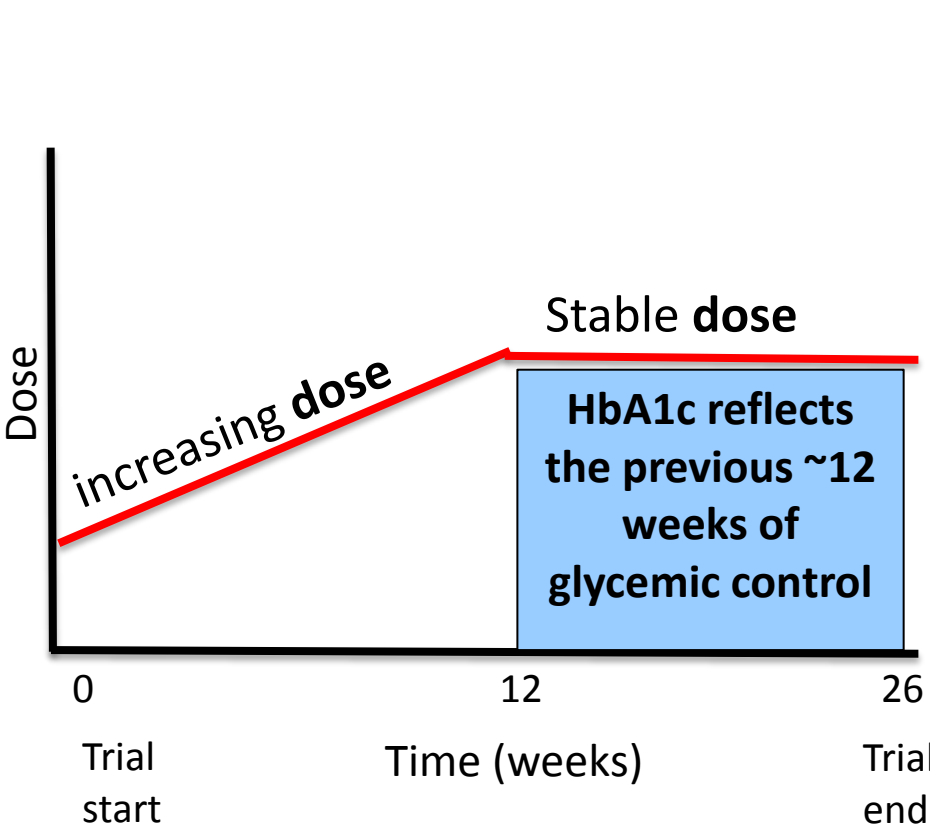
Time to Maximal Effective Dose of a Titratable Drug



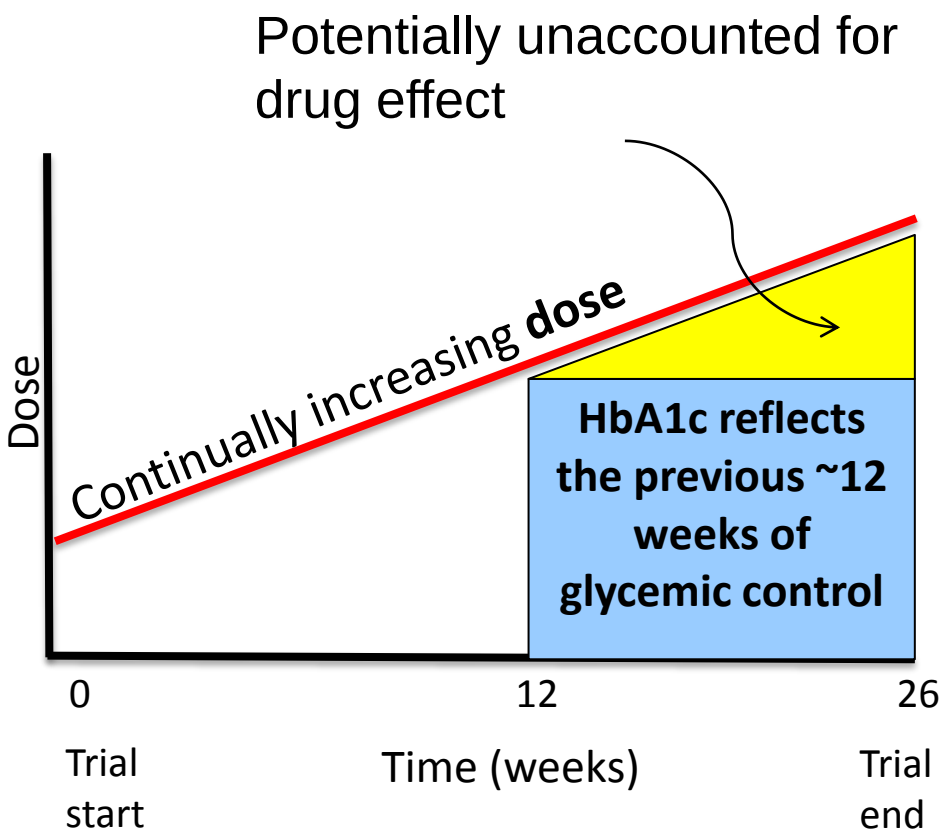
Interpretation of Change in HbA1c Titratable Drug



Interpretation of Change in HbA1c Titratable Drug



Potentially unaccounted for drug effect

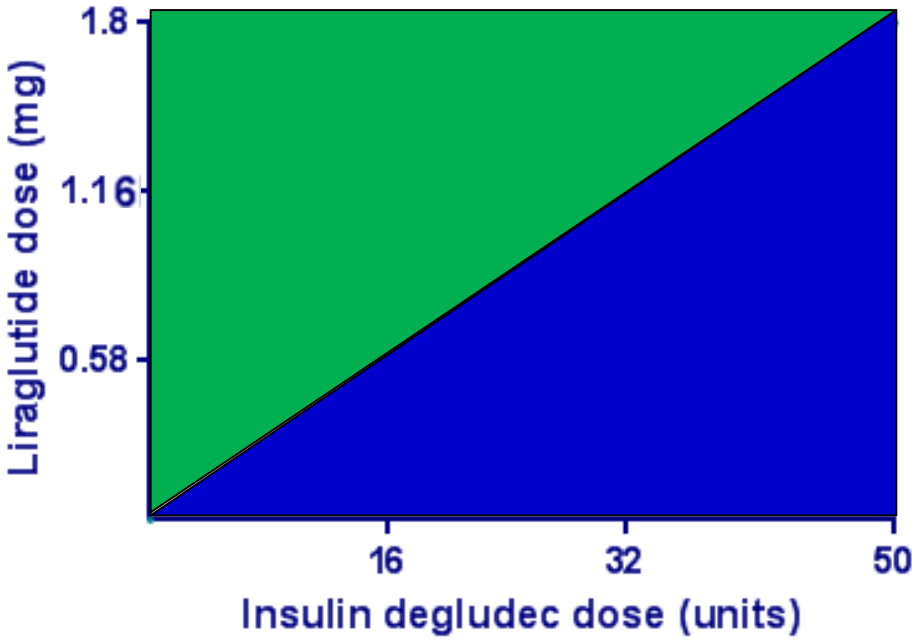


Interpretation of Change in HbA1c IDegLira Trials

- Imbalances in time to dose stabilization for insulin comparator uncapped studies
  - Time to dose stabilization: the time when the dose is no longer changing
- Factors causing imbalance in time to dose stabilization
  - The same titration algorithm for a one-drug vs. two-drug product (titration algorithm ignores one drug)
  - Conservative rate of titration
  - Low SMPG goals relative to usual clinical practice

Same Titration Algorithm for One Drug vs. Two Drugs

- Titration of one active drug product ≠ titration of two active drug products:
  - **IDegLira**: 2 units of IDeg +0.072 mg of liraglutide
  - **Insulin comparator**: 2 units of insulin



The liraglutide component + same insulin dose as comparator will result in *relatively* more glucose lowering in the IDegLira arm (faster titration).

Conservative Rate of Titration

- The magnitude and limited number of titration steps in the titration algorithm result in a slower titration of the insulin comparator in the insulin comparator trials.

Phase 3 trials IDegLira program	
SMPG (MG/DL)	DOSE CHANGE (dose units)
Below goal	-2
At goal *	0
Above goal	+2
*Goal for 3697, 3912, 3851: 72-90 mg/dL Goal for: 3952: 71-90 mg/dL Goal for: 3951: 72-108 mg/dL	

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Basal insulin dose adjustment type 2 DM trials insulin degludec program (NDA 203314)	
SMPG (MG/DL)	DOSE CHANGE (dose units)
<56	Decrease by 4 U
<70	Decrease by 2 U
<90	No adjustment
<126	Increase by 2 U
<144	Increase by 4 U
<162	Increase by 6 U
≥162	Increase by 8 U

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- The magnitude and limited number of titration steps in the titration algorithm result in a slower titration of the insulin comparator in the insulin comparator trials.

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<144	Increase by 4 U
<162	Increase by 6 U
≥162	Increase by 8 U

Low SMPG Goals
Relative to Usual Clinical Practice

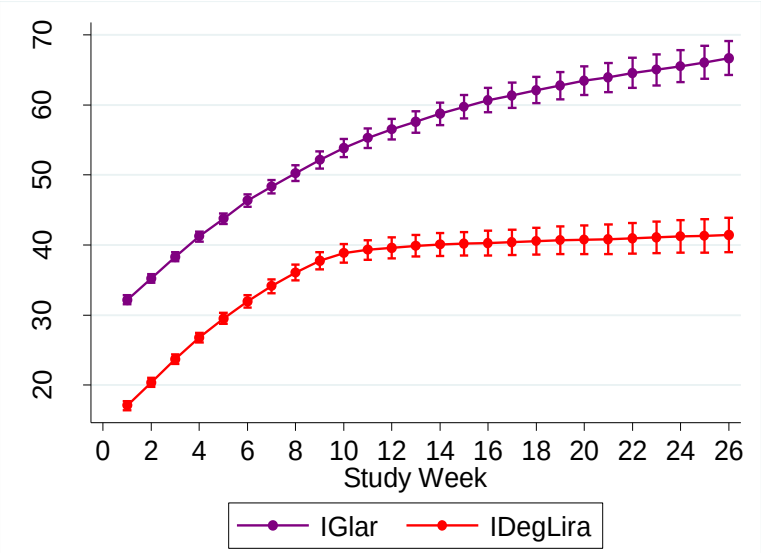
- Lower goals could contribute to a longer time to reach dose stabilization

Phase 3 trials SMPG fasting goals	
3697, 3912, 3851:	72-90 mg/dL
3952:	71-90 mg/dL
3951:	72-108 mg/dL

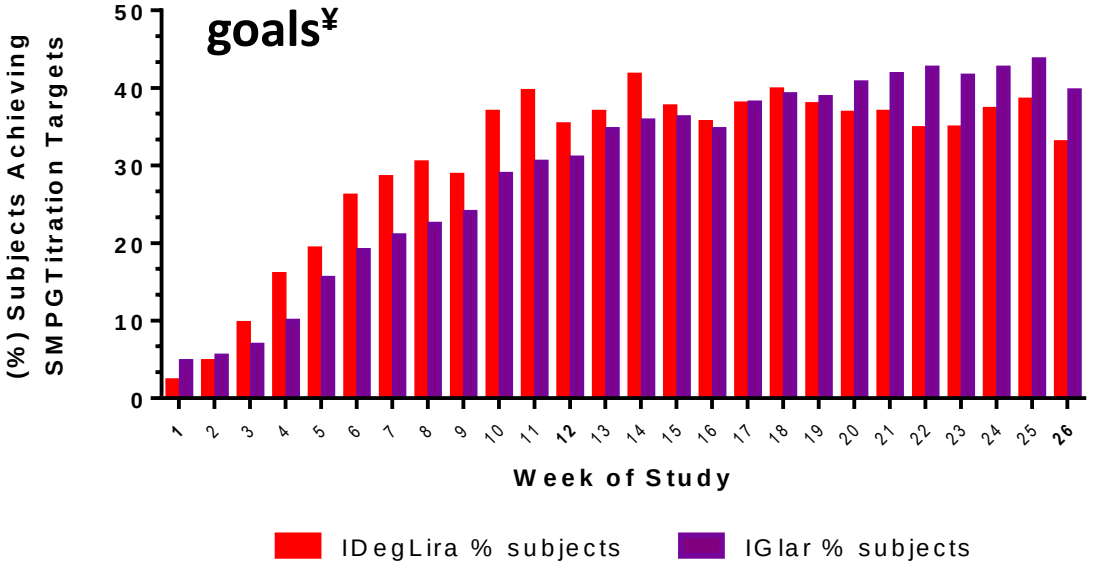
Dose Stabilization
IDegLira vs. Glargine

Trial 3952 Previous insulin glargine users

Insulin Dose by Week*



Proportion of subjects reaching glycemic goals¥



Median time to dose stabilization

IDegLira: week 12

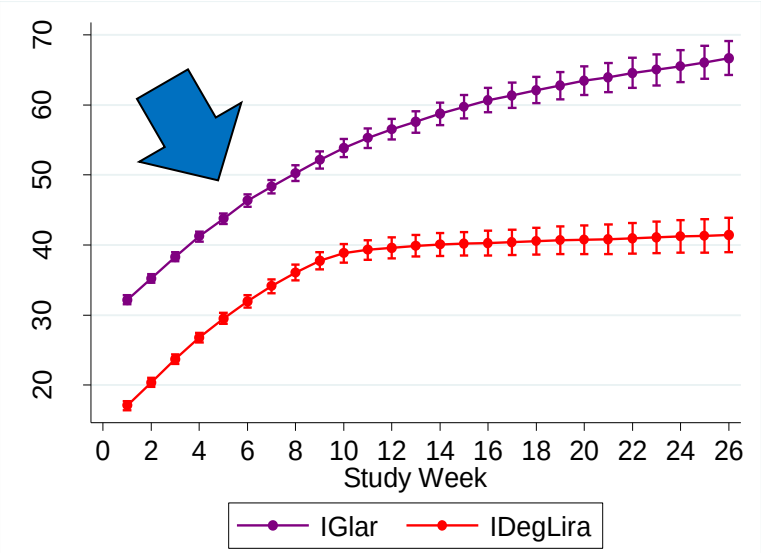
IGlar: week 19

*Results from MMRM analysis, ¥ refers to 71-90 mg/dL

Dose Stabilization
IDegLira vs. Glargine

Trial 3952 Previous insulin glargine users

Insulin Dose by Week*



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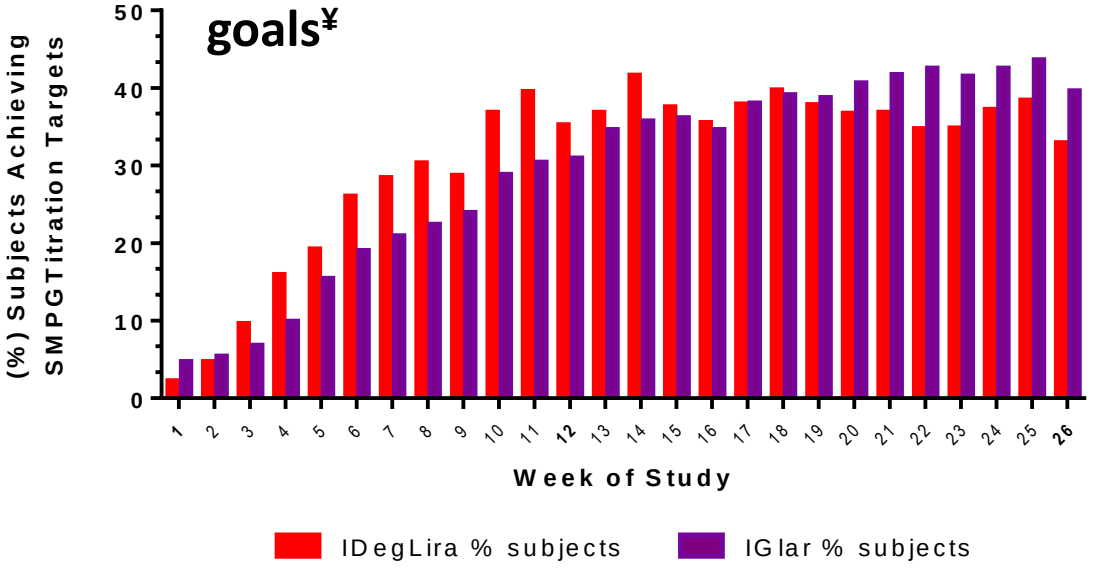

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Dose Stabilization
IDegLira vs. Glargine

Trial 3952 Previous insulin glargine users

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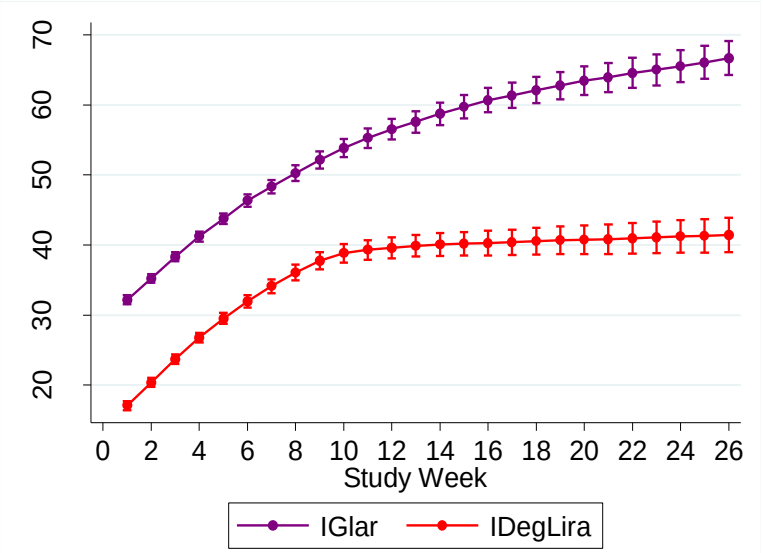

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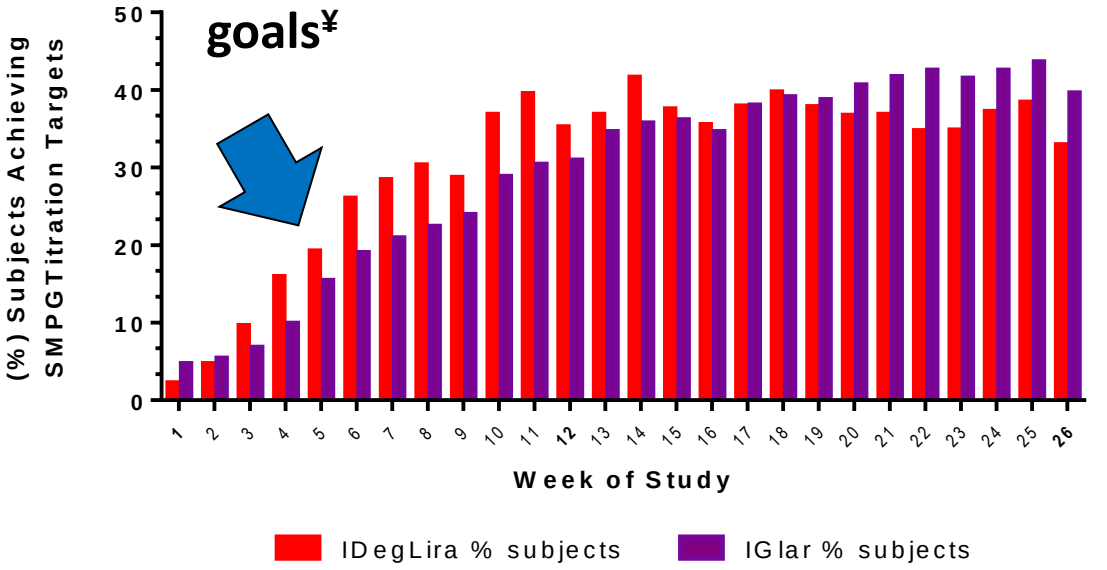

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IDegLira: week 12

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IDegLira vs. Glargine

Trial 3952 Previous insulin glargine users

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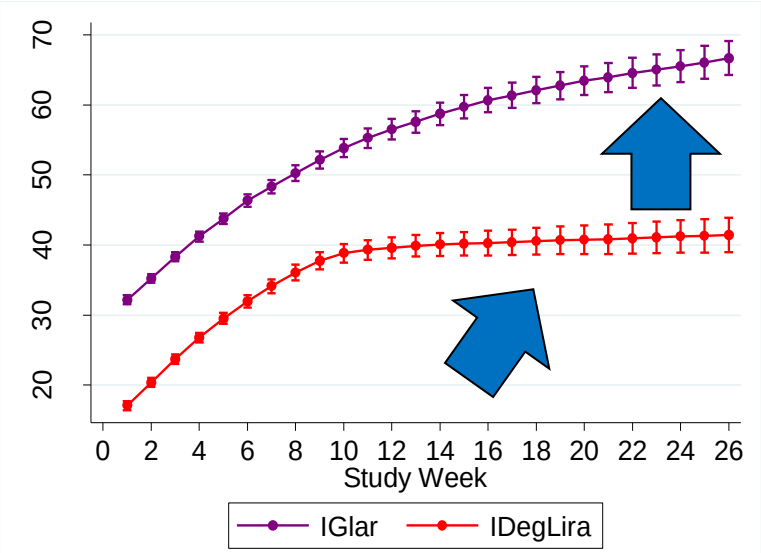

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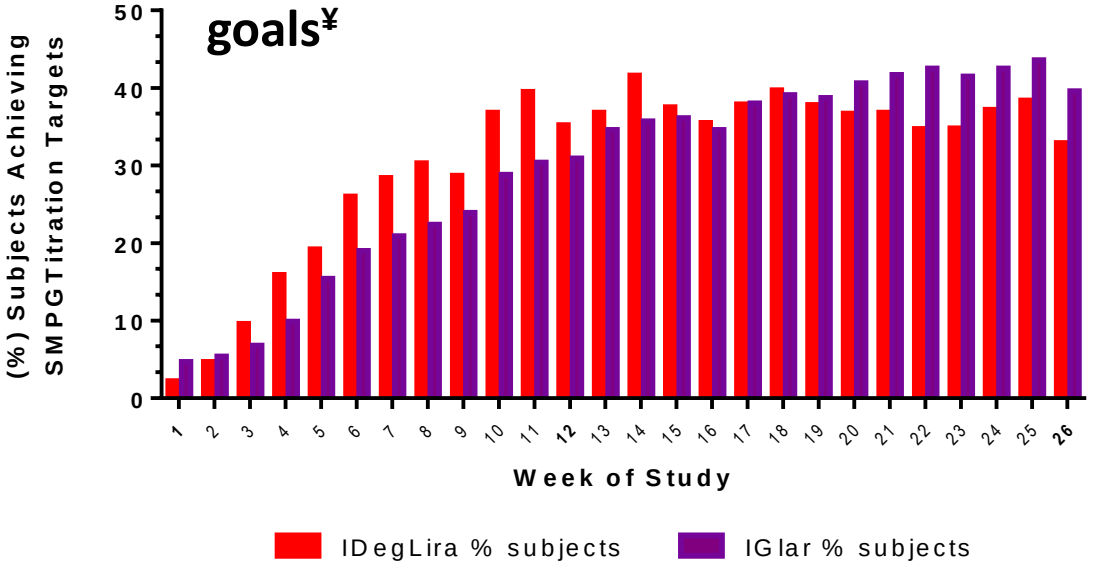

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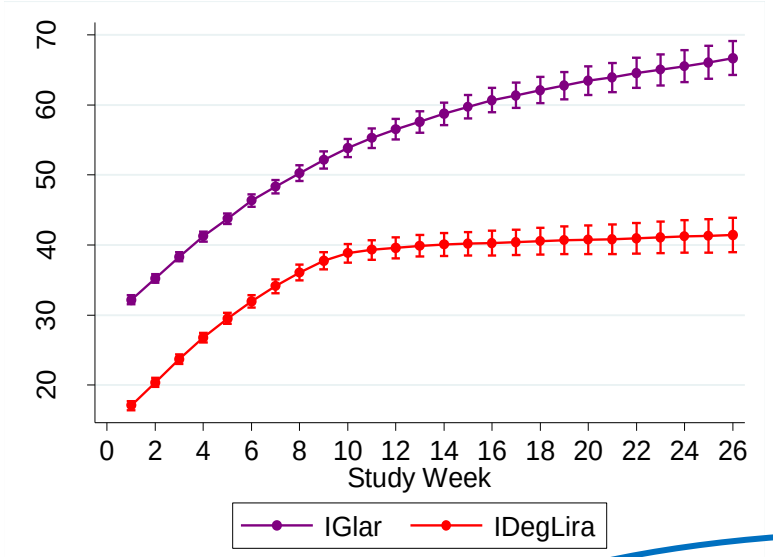

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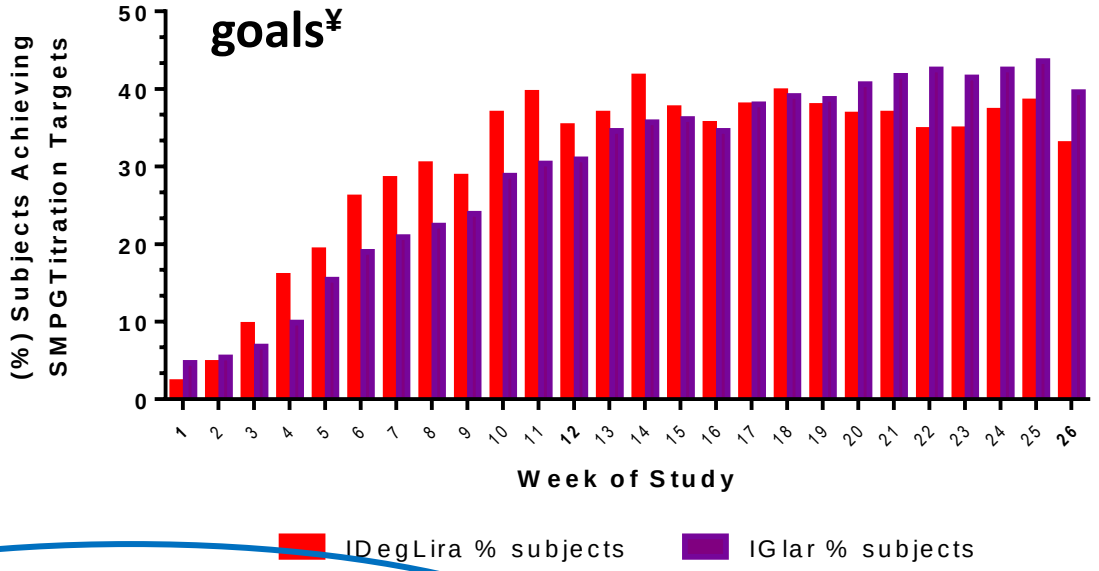


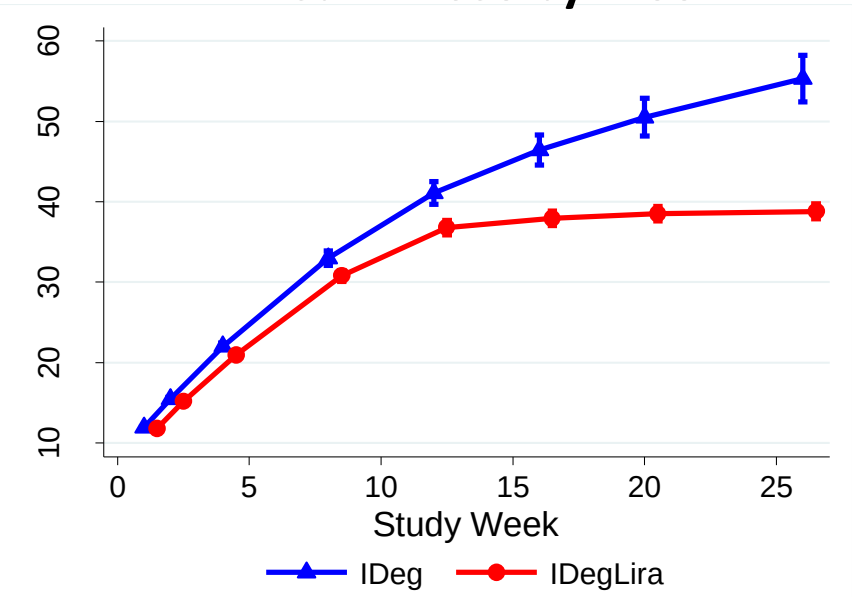
Median time to dose stabilization
IDegLira: week 12
IGlar: week 19

*Results from MMRM analysis, ¥ refers to 71-90 mg/dL

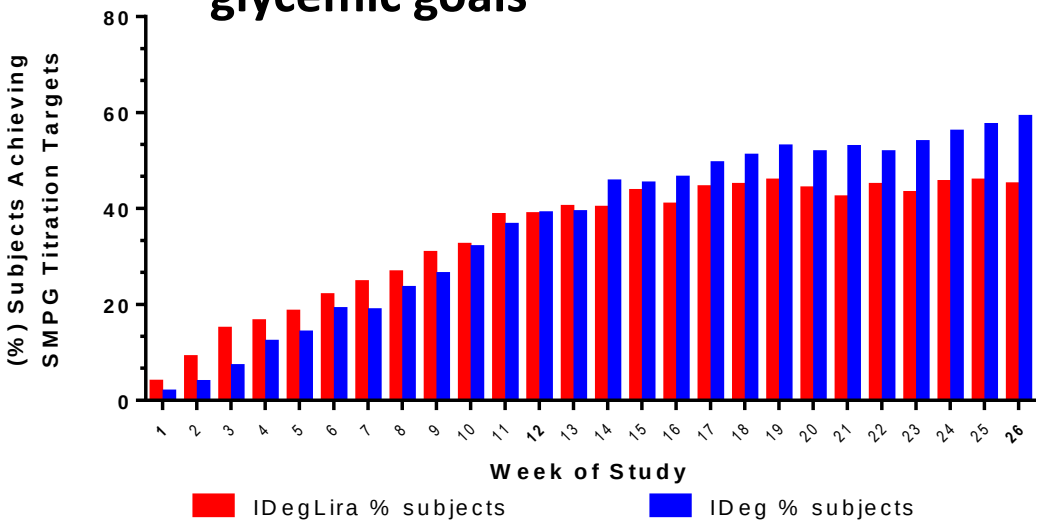
Dose Stabilization
IDegLira vs. IDeg

Trial 3697 Subjects not previously treated with GLP-1 or insulin

Insulin Dose by Week*



Proportion of subjects reaching glycemic goals¥



Median time to dose stabilization

IDegLira: week 15

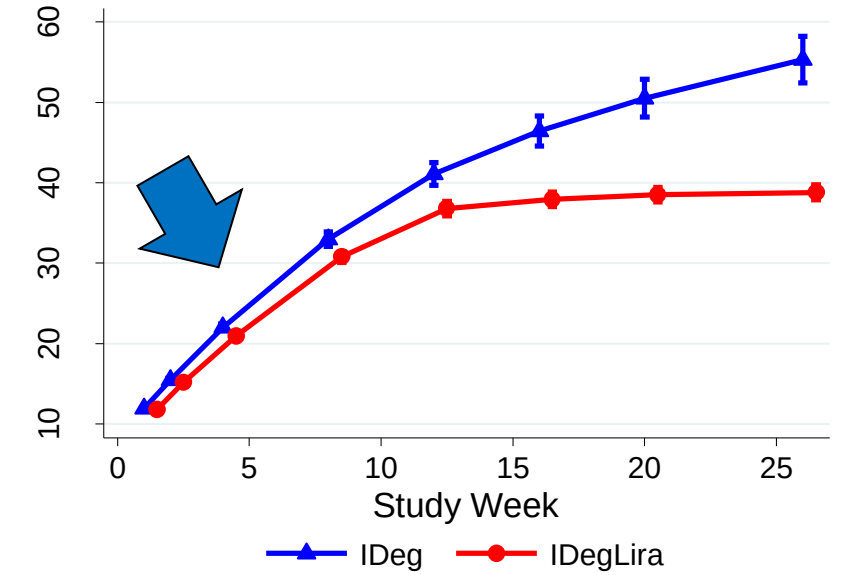
IDeg: week 26

*Results from MMRM analysis; ¥ refers to 70-90 mg/dL

Dose Stabilization
IDegLira vs. IDeg

Trial 3697 Subjects not previously treated with GLP-1 or insulin

Insulin Dose by Week*



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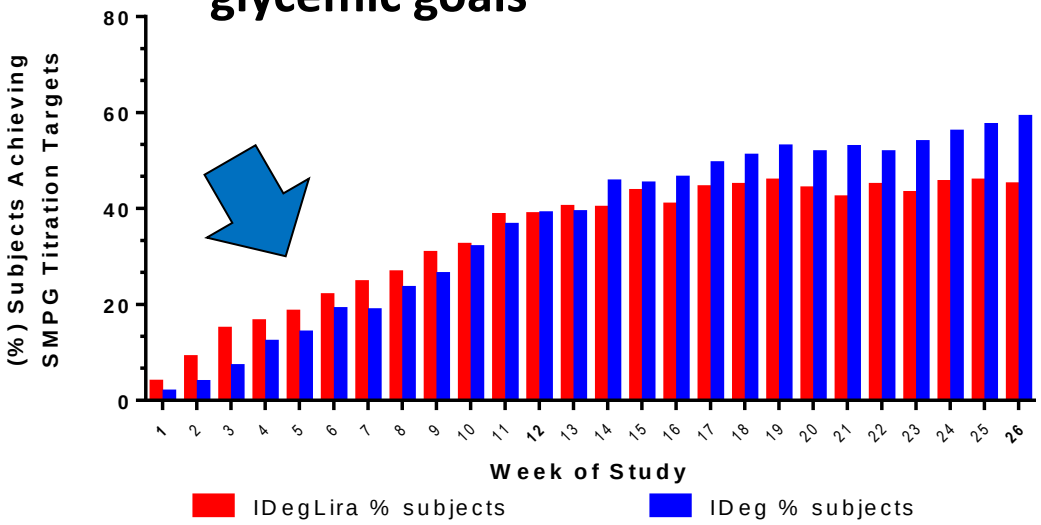

Median time to dose stabilization

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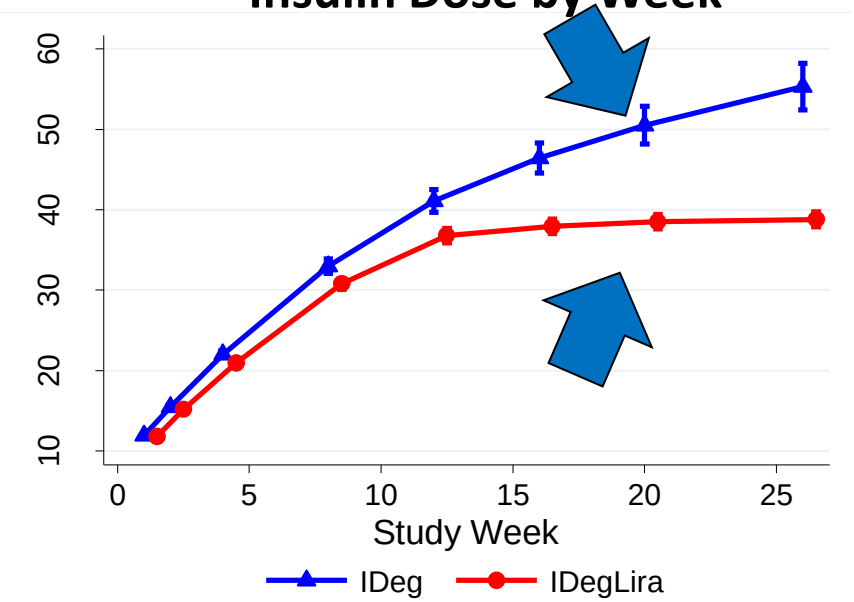
IDeg: week 26

*Results from MMRM analysis; ¥ refers to 70-90 mg/dL

Dose Stabilization
IDegLira vs. IDeg

Trial 3697 Subjects not previously treated with GLP-1 or insulin

Insulin Dose by Week*



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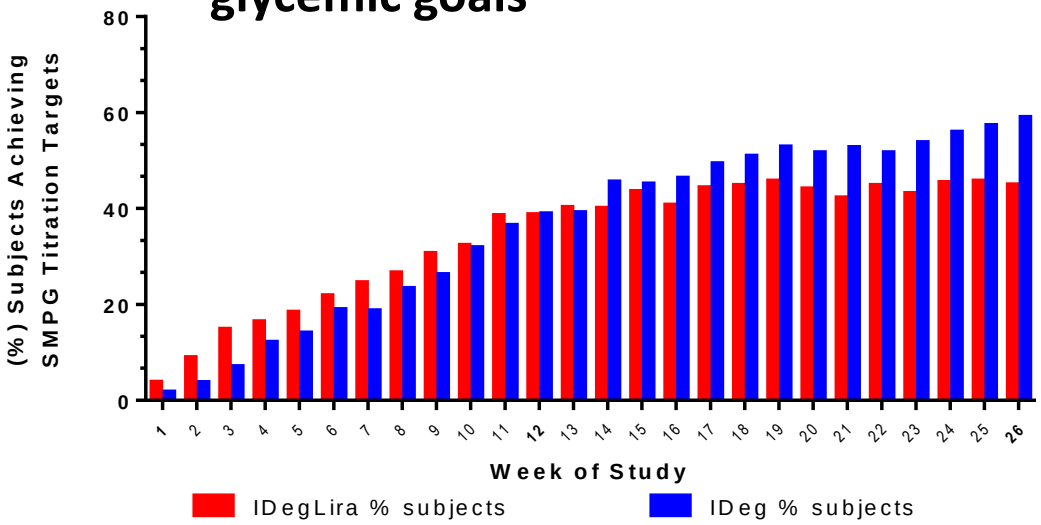

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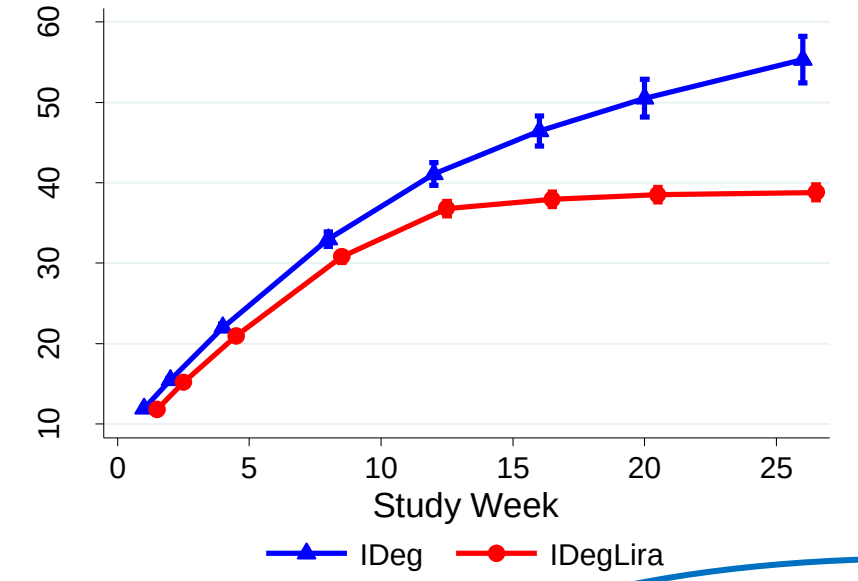

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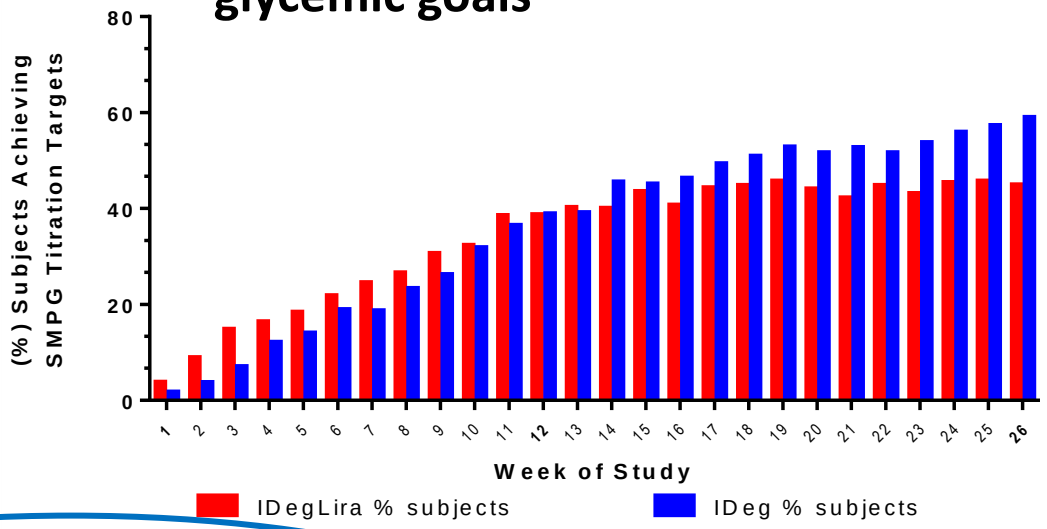

Median time to dose stabilization
IDegLira: week 15
IDeg: week 26

*Results from MMRM analysis; ¥ refers to 70-90 mg/dL

Challenges in Interpreting HbA1c Results in the Non-capped Trials

- Stable HbA1c needed for fair between-arm comparison
- Aspects of the dosing regimen did not result in stable HbA1c by week 26
  - Insulin still being titrated in the insulin comparator arm for many patients after week 12
- While statistical superiority was demonstrated, external validity is unclear
  - Would IDegLira be superior to insulins if they had been fully titrated by week 26

Generalizability of the Results of the IDegLira Trials to Clinical Practice

- IDegLira development program appears to have demonstrated contribution to claimed effect (glycemic control) for both components
- Generalizability to clinical practice is limited by trial design (dose cap trial) and or dosing issues (non-cap trials)

Liraglutide Dosing

- Contribution to claimed effect based on overall trial results (not based on consideration of a minimum effective dose of liraglutide)
- 0.6 mg is the starting dose
- The minimum approved effective dose for glycemic control is 1.2 mg
- Concern that subjects receiving less than the minimum clinically effective dose of liraglutide may not derive glucose-lowering benefit from the liraglutide component of IDegLira but may be exposed to risks associated with liraglutide use

Proportion of Patients Not Reaching At Least 0.6 and 1.2 mg of Liraglutide

Dose of IDegLira ≤ 16 Dose of Liraglutide ≤0.58	
Trial 3912	1%
Trial 3952	1%
Trial 3851	3%
Trial 3697	8%
Trial 3951	27%

Dose of IDegLira ≤32 Dose of Liraglutide ≤1.16	
Trial 3912	10%
Trial 3851	14%
Trial 3952	22%
Trial 3697	31%
Trial 3951	65%

Trials 3912: IDegLira vs. IDeg (capped trial), 3952: IDegLira vs. IGlar; 3851: IDegLira vs. GLP-1; 3697: IDegLira vs. IDeg and liraglutide; 3951: IDegLira vs. placebo

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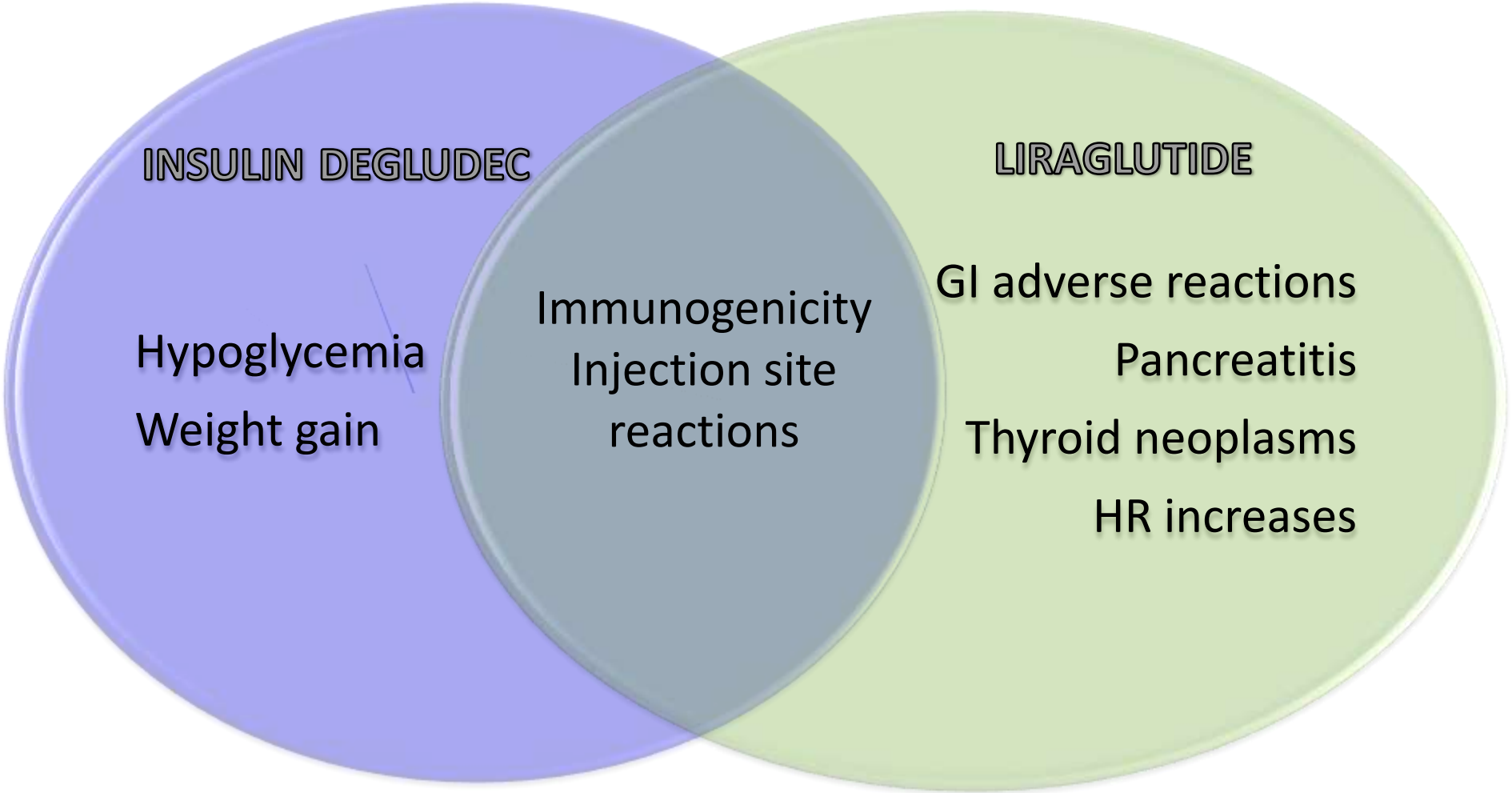
Presentation Overview

- Background and product overview
- Phase 3 trial designs
- Statistical Efficacy – Anna Kettermann
- Clinical relevance
- Safety findings

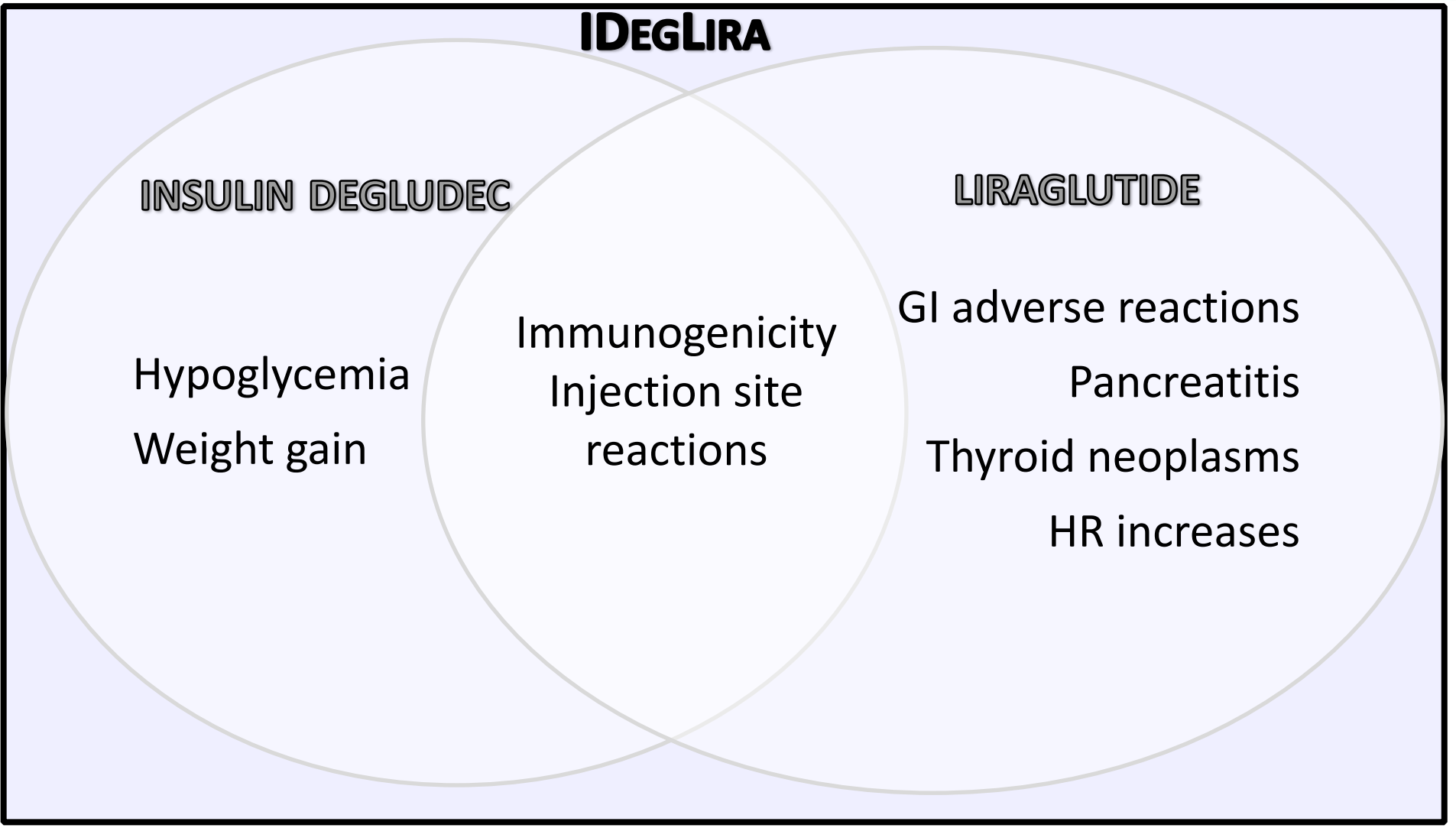
Safety Program Objectives
Combination Drug

- Evaluate any new risks that may result from the combination
  - Safety profile individual components has been already characterized
  - Victoza already studied with basal insulin

Drug Related Risks



Drug Related Risks



Safety Analyses

- Data from all five phase 3 trials were pooled
- 4 treatment groups were considered for safety analyses

Safety Group	Source of data
IDegLira	IDegLira arm from all 5 completed trials
Basal Insulin	Combined data for IDeg arm of Trials 3697-ext and 3912, and IGlar arm of Trial 3952
GLP-1	Combined data for liraglutide arm in Trial 3697-ext and liraglutide/exenatide arm in Trial 3851
Placebo	placebo arm from Trial 3951

Source: Integrated Summary of Safety, page 33, Table 1-4.

IDegLira Population

BASELINE CHARACTERISTICS OF PATIENTS EXPOSED TO IDEGLIRA	
	N
Safety analysis set	1881
Male	53%
Age group (years)	
≥ 18 to ≤ 65 years	80%
≥ 65 years	20%
White	75%
Not Hispanic or Latino	84%
United States	32%
Duration of diabetes <10 years	64%
BMI group (kg/m^2)	
≤ 25	9%
25 – 30	29%
30 - 35	35%
≥ 35	28%
Renal function*	
Normal	50%
Mild impairment	44%
Moderate impairment	6%

*Renal function is classified using creatinine clearance estimated using the CKD-EPI equation

Source: modified integrated Summary of safety, Table 1-8, page 42-43

Major Safety Findings

Completed trials

	IDegLira N= 1881	Basal insulin N= 890	GLP-1 N= 557	Placebo N= 146
Deaths	0.2 %	<0.1%	--	--
SAE	3.9%	5.3%	4.3%	2.7%
Dropouts Due to AE	1.7%	2.2%	6.5%	0.7%

SAE: Serious adverse event, AE: adverse event

Most Frequent Adverse Events Leading to Dropouts

	IDegLira N=1881	Basal Insulin N=890	GLP-1 N=557	Placebo N=146
Dropouts Due to AE	1.7%	2.2%	6.5%	0.7%
Gastrointestinal disorders	0.4%	0	2.7%	0
Investigations	0.4%	0.8	1.6%	0
General disorders and administration site conditions	0.3%	0.1%	0	0
Nervous system disorders	<0.1%	0.5%	0.4%	0

MedDRA classification shown by system organ class (SOC)

Gastrointestinal Adverse Reactions >3% in IDegLira Group

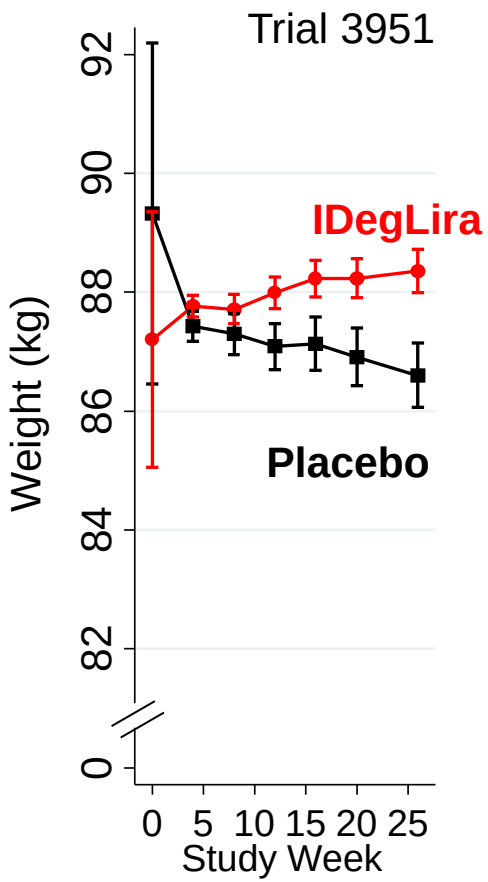
	IDegLira N= 1881	Basal insulin N= 890	GLP-1 N= 557	Placebo N= 146
Gastrointestinal disorders SOC	25%	14%	34%	23%
Diarrhea	8%	4%	11%	9%
Nausea	8%	3%	15%	6%
Vomiting	4%	2%	7%	4%
Dyspepsia	3%	1%	4%	1%

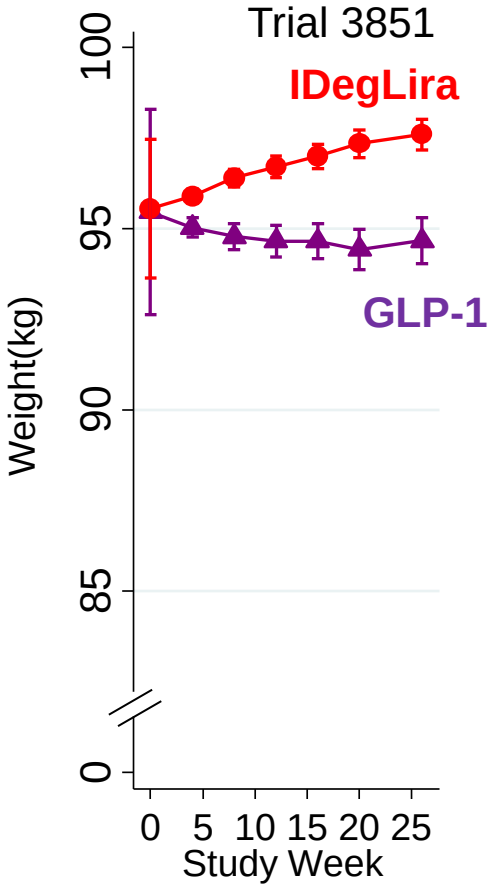
Source: modified information request 22 October 2015, rounded to whole number

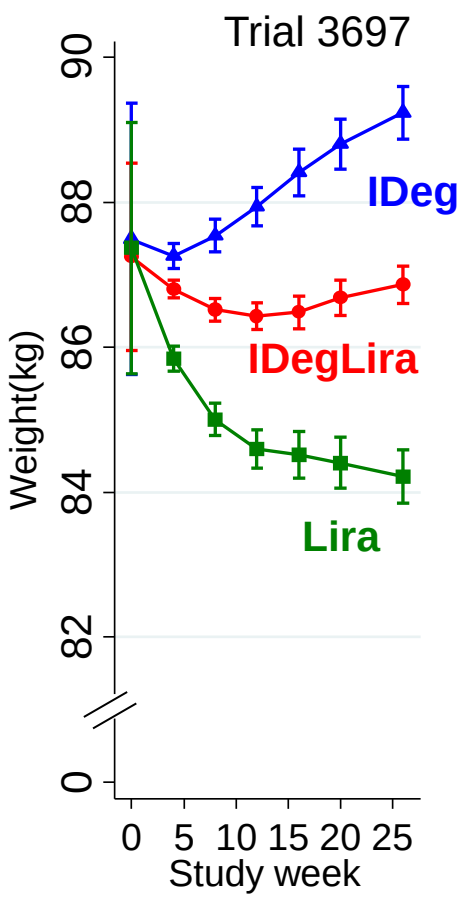
Body Weight

- Body weight increase is a risk with some antidiabetic therapies
- Insulin is generally associated with increased body weight
- GLP-1 agonist therapy is generally associated with modest weight reduction
- In the IDegLira program, change in body weight was investigated as a secondary endpoint

Changes in Body Weight







Limitations of Body Weight Change Analyses

- Modest changes in weight (~1.5kg)
- Trials did not capture the clinical meaning of weight difference
- 26- week duration is relatively short duration for weight studies
- Uncertain what these weight changes mean in the overall health or quality of life of subjects

Severe Hypoglycemia*

Phase 3 trials including 52 week data

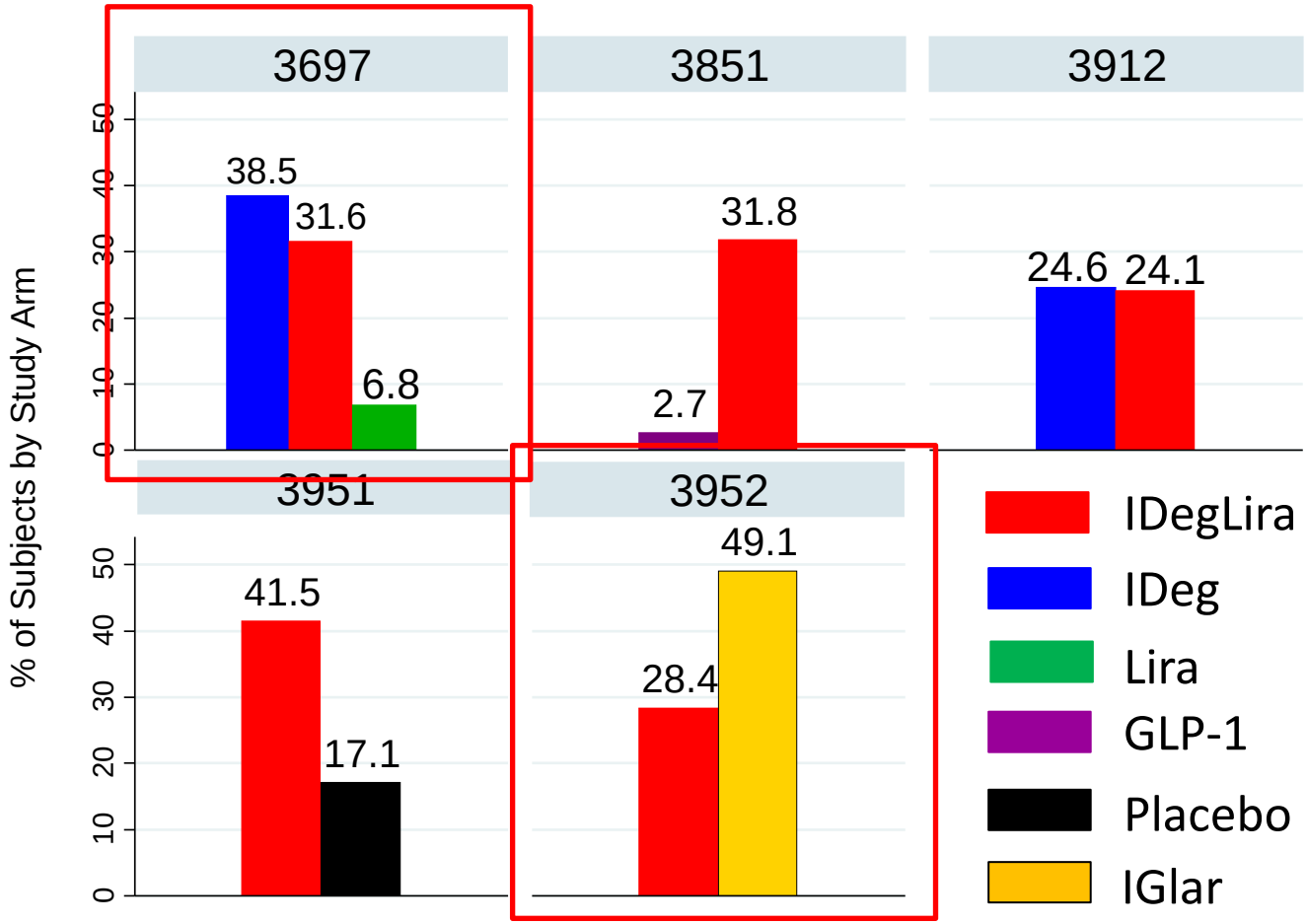
	IDEGLIRA	BASAL INSULIN	GLP-1	PLACEBO
	N (%)	N (%)	N (%)	N (%)
Trial 3697*	3(0.4)	2(0.5)	2(0.5)	-
Trial 3912	1(0.5)	0	-	-
Trial 3851	1(0.3)	-	0	-
Trial 3951	2(0.7)	-	-	0
Trial 3952	0	1(0.4)	-	-

Safety analysis set
*Includes data for the 52 week
N: Number of Subjects; %: Percentage of Subjects with the Event; all subjects experienced one case of severe hypoglycemia

***Severe hypoglycemia:** an episode requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

Source: 3697: table 14.3.1.45; 3912: CSR, table 14.3.1.46; 3851 CSR:, table 14.3.1.47; 3951 CSR:, table 14.3.1.46; 3952 CSR: table 14.3.1.47.

Novo Nordisk Definition Hypoglycemia*



***Novo Nordisk's hypoglycemia** - composed of ADA severe and minor hypoglycemic episodes. Minor hypoglycemic episodes are episodes with symptoms consistent with hypoglycemia with a plasma glucose < 56 mg/dL and which was handled by the subject himself/herself or any asymptomatic plasma glucose value 56 mg/dL or full blood glucose value < 50 mg/dL.

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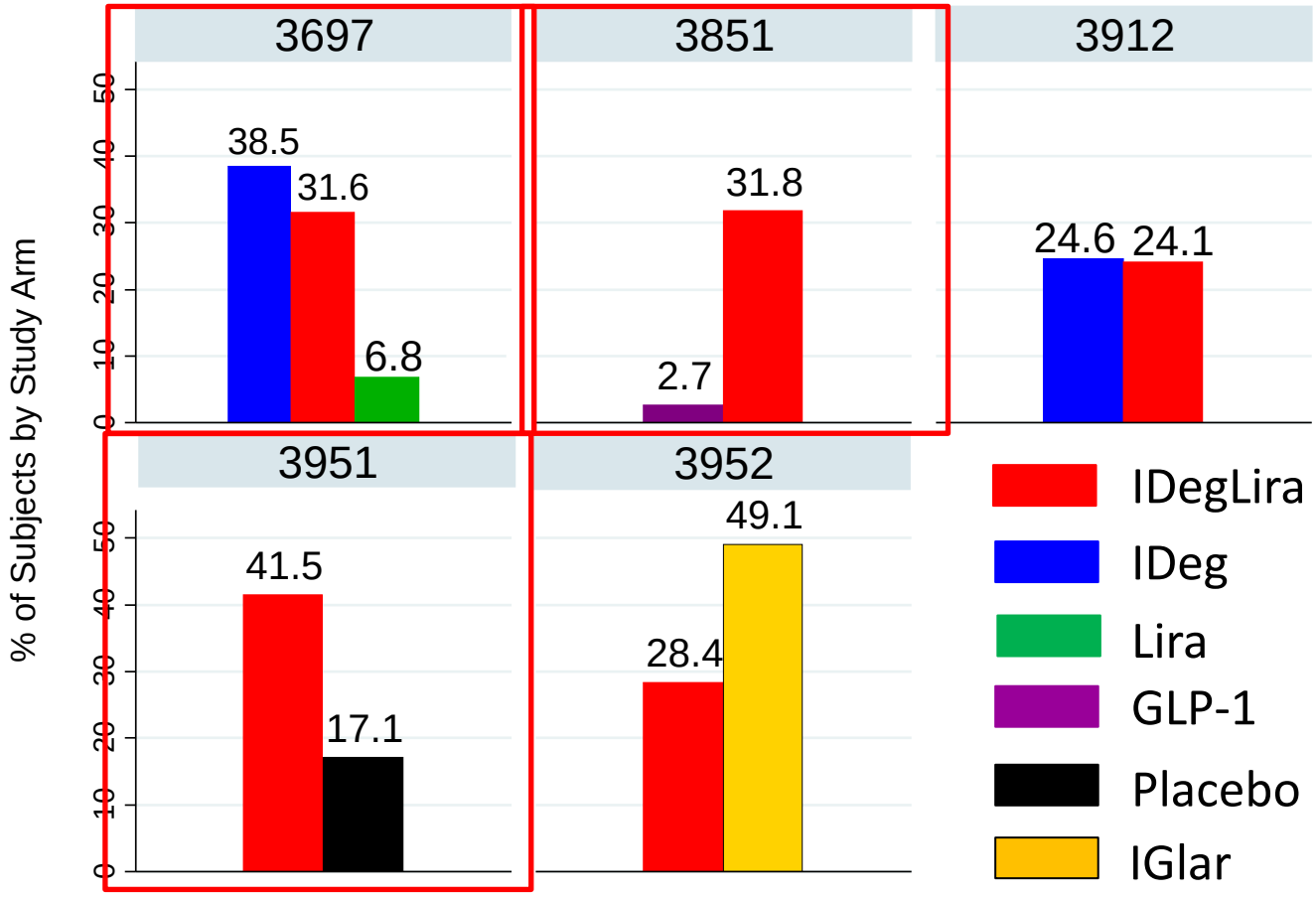

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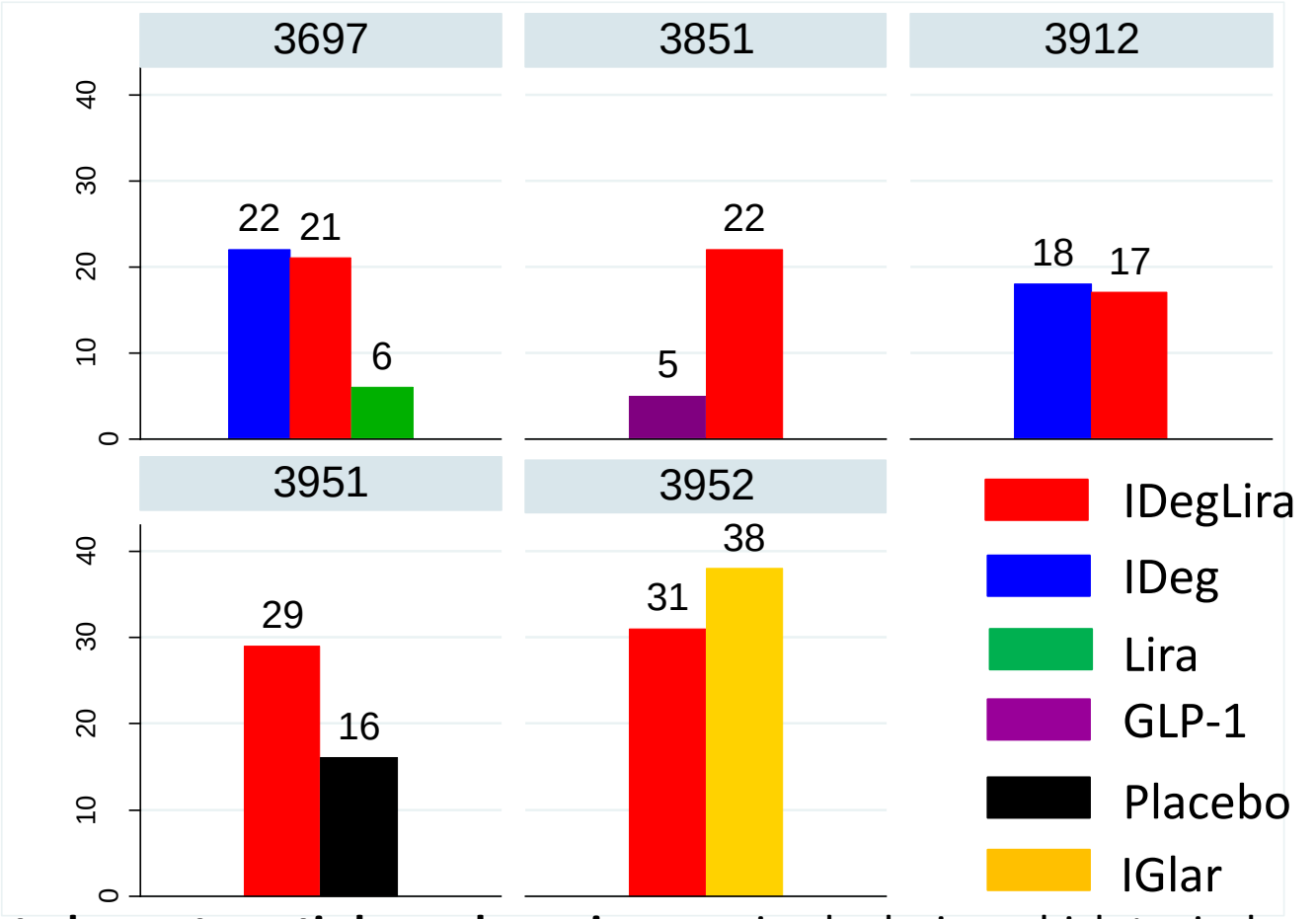
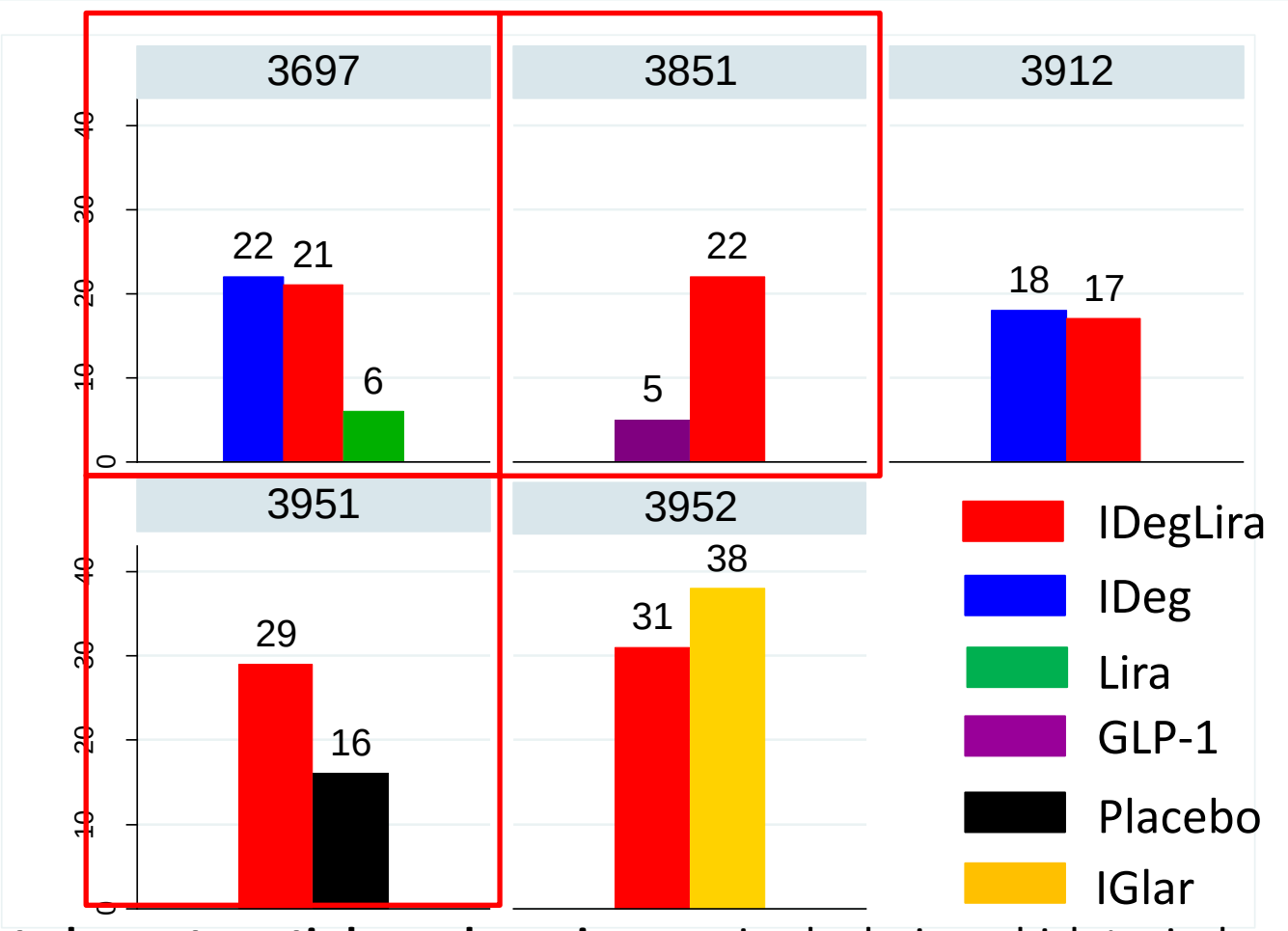
ADA Documented Symptomatic Hypoglycemia*



***Documented symptomatic hypoglycemia:** an episode during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL

ADA Documented Symptomatic Hypoglycemia*



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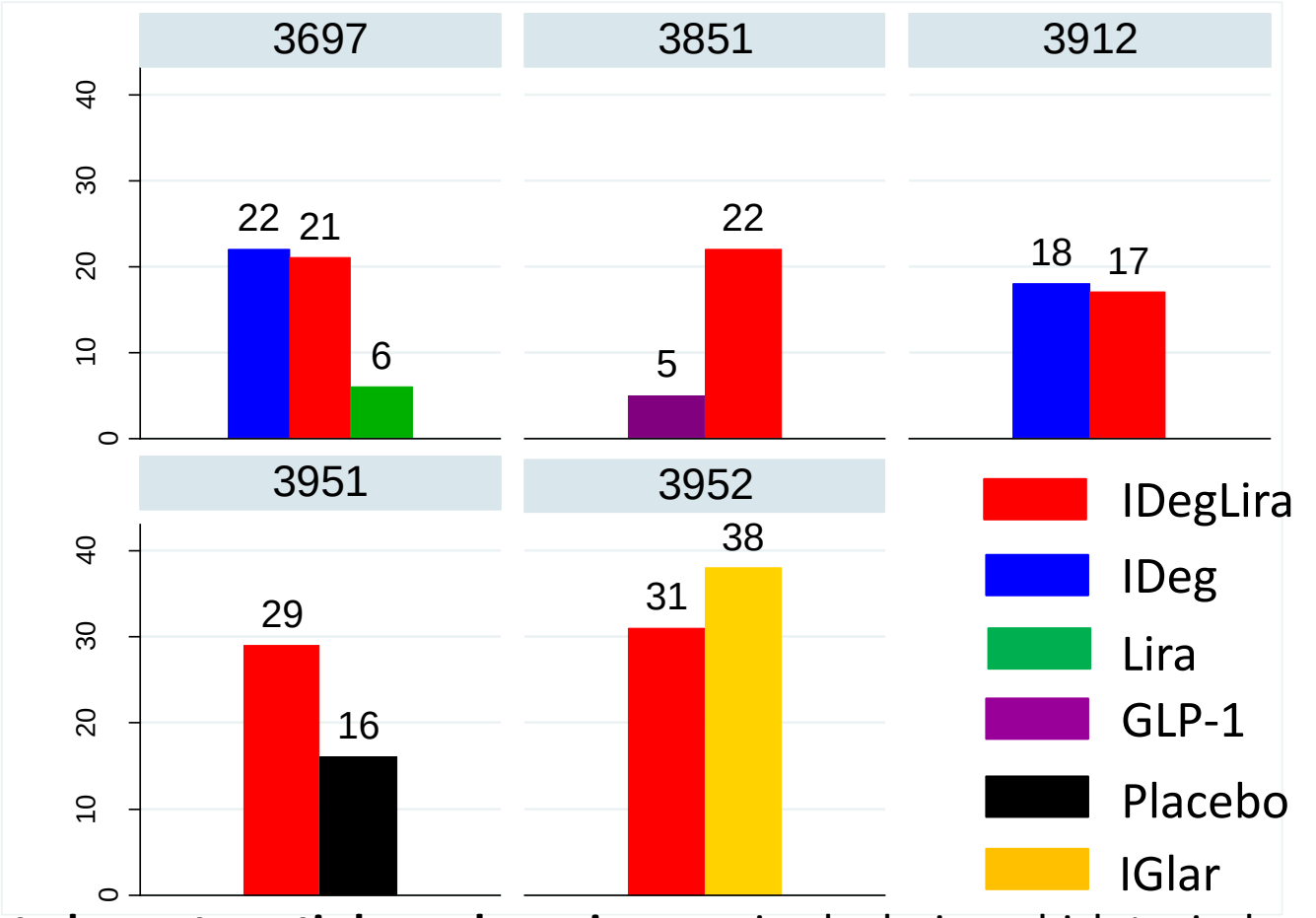

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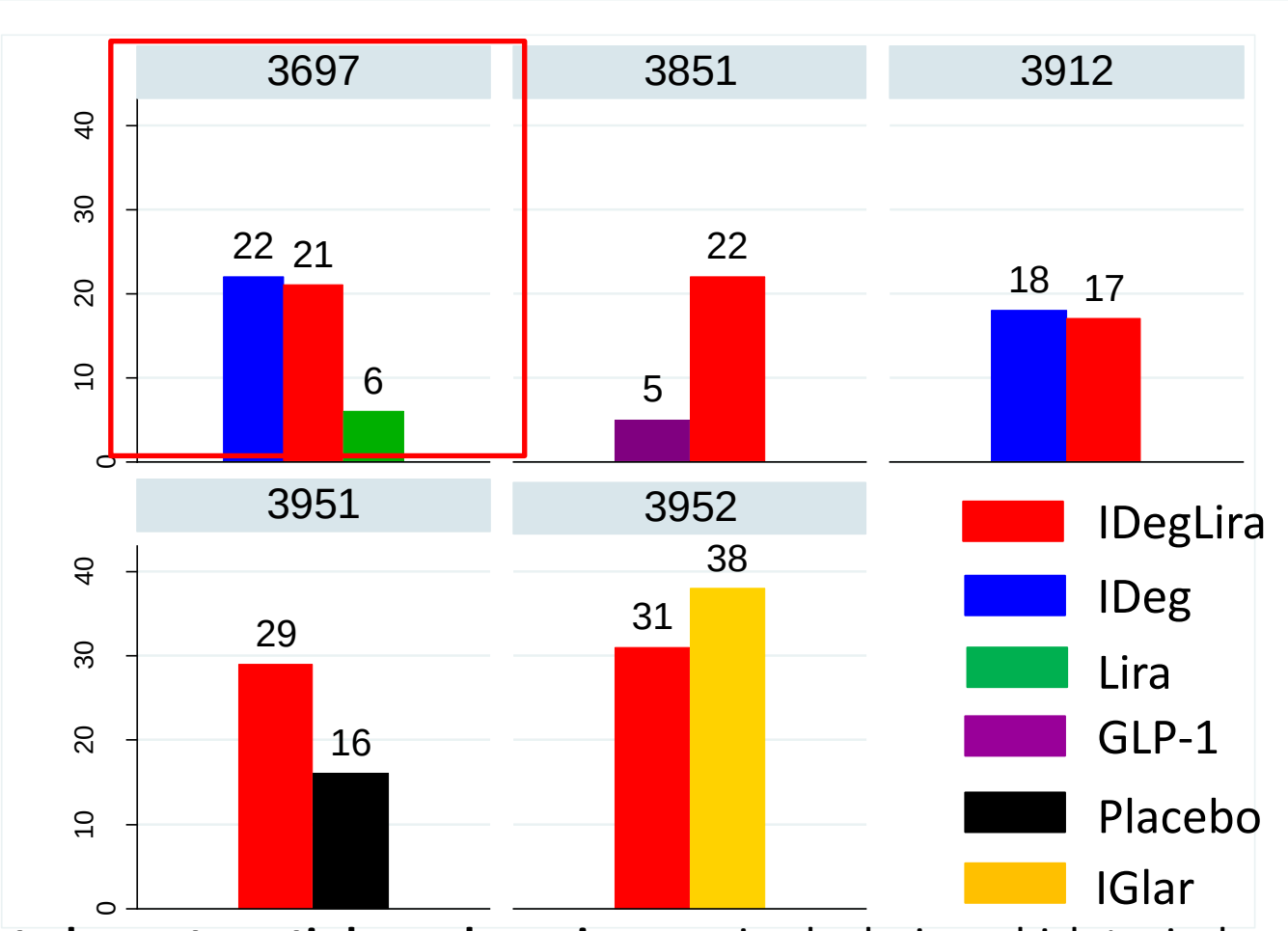

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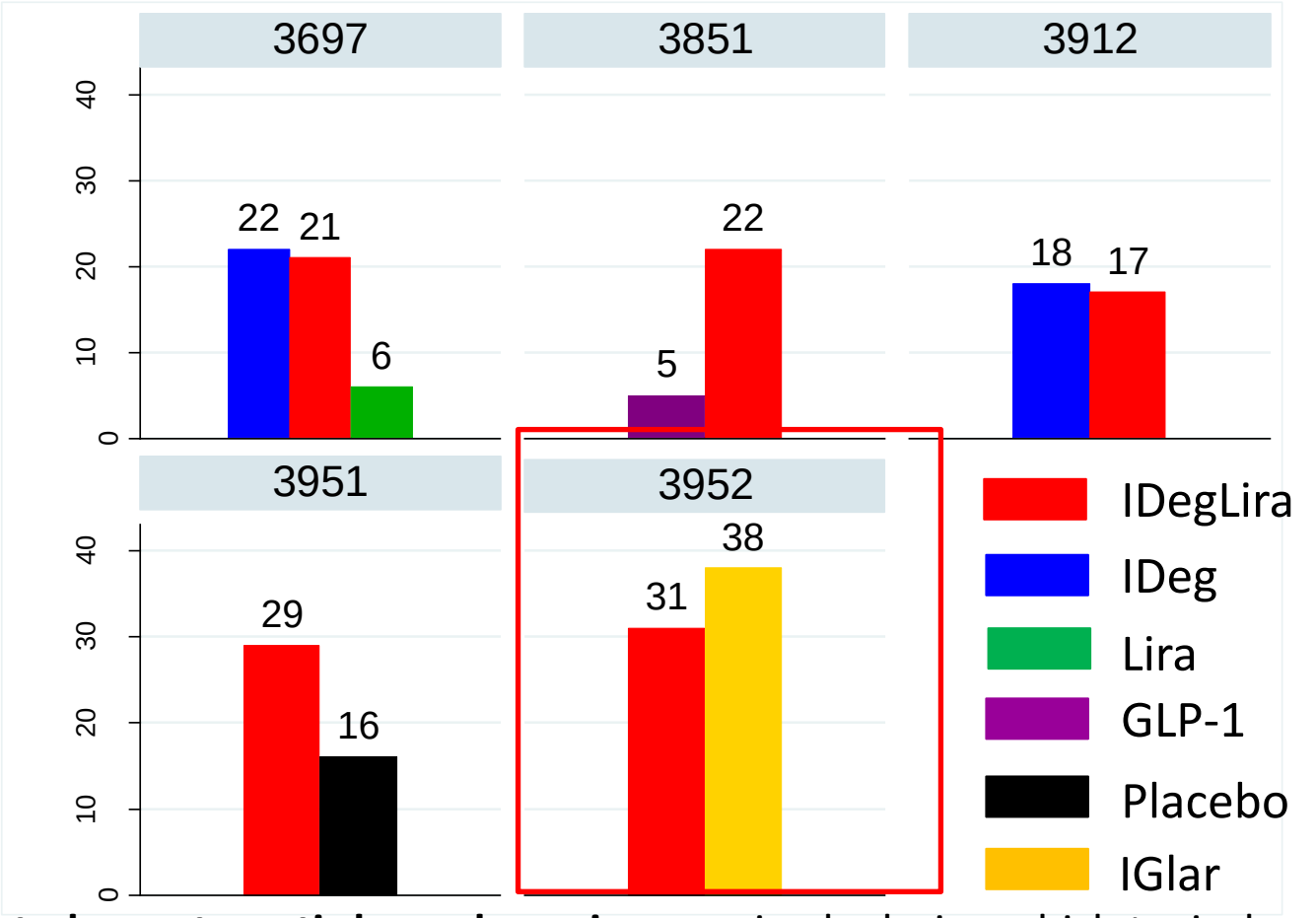

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Summary of Hypoglycemia Data

- Few events of severe hypoglycemia
- Less hypoglycemia with Novo Nordisk definition when compared to insulin comparators
- Attenuated with the ADA documented symptomatic definition vs. insulin comparators
- More hypoglycemia than placebo or GLP-1 comparator

Limitations of the Hypoglycemia Analyses

- Hypoglycemia definitions other than 'severe' subject to reporting bias in open-label trials
- Endpoints based on glucometer derived data
  - Reliability of measurements
- Trials did not capture the clinical meaning of observed differences in hypoglycemia rates
  - No difference in severe hypoglycemia
- Uncertain what the data mean in the overall health or quality of life of subjects

Other Safety Findings

- Pancreatitis and thyroid neoplasms were rare, with no clinically significant difference between IDegLira and comparators
- IDegLira, similar to liraglutide, had a 2-3 beat heart rate increase compared to placebo.
- There were no clinically important differences of immunogenicity or injection site reactions for IDegLira vs. comparators

Summary

- Five phase 3 trials met the pre-specified glycemic primary endpoints
- Questions regarding external validity
- Potential issues related to loss of dosing 'flexibility'
- For previous insulin or GLP-1 users a reasonable proportion reached liraglutide doses of at least 1.2 mg
  - For patients not previously treated with insulin or GLP-1 the proportions were lower

Summary

- Safety of IDegLira reflects the safety profile of its components
  - Weight gain (insulin)
  - Hypoglycemia (insulin)
  - Gastrointestinal adverse reactions and heart rate increases (liraglutide)
- No unexpected safety issues identified
- Potential safety issues related to the product presentation (pen device) discussed in the next presentation

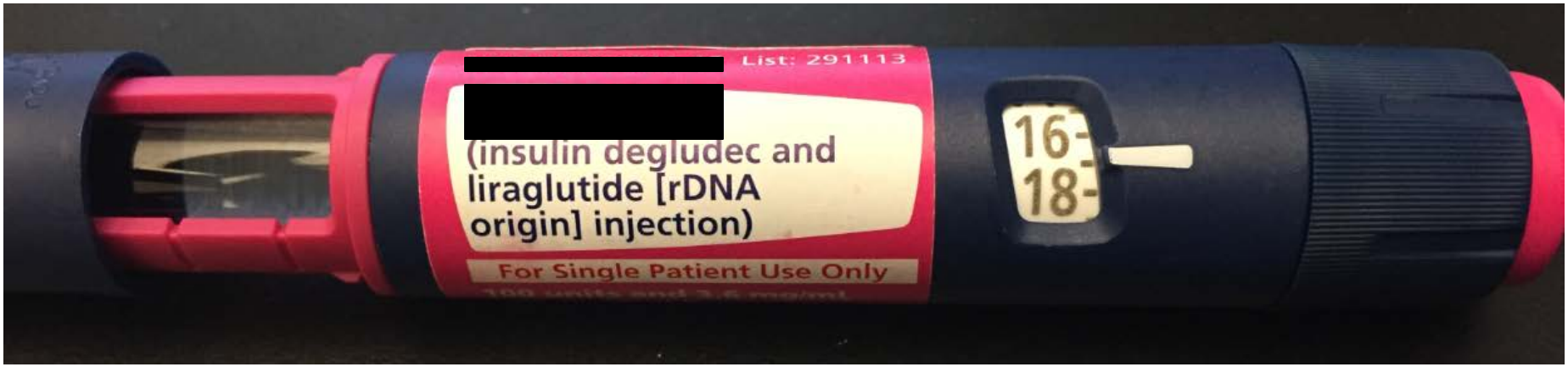
Human Factors Evaluation

Objectives

- Describe the product characteristics for insulin degludec and liraglutide (IDegLira)
- Provide a brief overview of human factors testing
- Summarize the results from the human factors testing conducted for IDegLira

IDegLira Product Overview

- Fixed-ratio multi-ingredient product containing a long-acting insulin and a GLP-1 receptor agonist
  - 100 units/mL of insulin degludec to 3.6 mg/mL of liraglutide
  - Pen designed to deliver doses from 1 to 50 in a single injection with dose increments of 1, with each increment containing 1 unit insulin degludec and 0.036 mg liraglutide



Review Considerations for IDegLira

1. The two active ingredients are not dosed using the same terms of measure (units vs. mg)
   - Pen device dials doses based on the units of insulin degludec only
   - How best to refer to dosing units without misrepresenting the product contents
   - The use of both terms and the lack of measurement terms may confuse users
2. The risk for drug duplication if users are not aware of both active ingredients
3. Dosing limited to a maximum of 50 units of insulin degludec

Human Factors Testing

- **Purpose:** To demonstrate that the device can be used by the intended users without serious use errors or problems, by the intended uses, and under the expected use conditions.
- The testing should be designed as follows:
  - The test participants represent the intended users of the device (≤15 participants per distinct user group)
  - All critical tasks are performed during the test
  - The device user interface represents the final design
  - The test conditions simulate actual conditions of use
- Data received is reviewed to determine if changes to the product design and/or product labeling are necessary for risk reduction

IDegLira Human Factors Study

IDegLira Human Factors Study Design

- Study designed to evaluate the ability of the intended users to properly use the IDegLira pen injector, including dialing and administering a dose
- Training included 30 minutes of one-on-one, hands-on training with a certified diabetes educator and a training video
  - 63 patients were trained
- 174 representative users
  - 16 physicians, physician assistants (PA), nurse practitioners (NP)
  - 15 pharmacists
  - 15 nurses
  - 64 adult patients with diabetes (31 pen-experienced & 33 pen-naïve)
  - 64 elderly patients with diabetes (31 pen-experienced & 33 pen-naïve)

Human Factors Study Tasks

1. **Product Differentiation Tasks**: Participants were presented with multiple pen injector cartons (task 1) and pen injectors (task 2) and instructed to select the test product
2. **Product Handling Tasks**: Participants were presented with a carton of pen injectors, the instructions for use (IFU), and other materials to simulate injection administration
3. **Instructions for Use (IFU) Evaluation Exercise**: All trained participants and those untrained participants that interacted with the IFU were asked to interpret two excerpts from the IFU after completing the handling tasks

Summary of Human Factors Study Results

1. **Product Differentiation**
   - Failures attributed to participant confusion regarding the task rather than poor differentiation among the products
2. **Product Handling**
   - Failure to prime and failure to prime correctly were the most common errors
   - Errors might result in clinically insignificant under doses
   - These errors are common to this device platform
3. **IFU Evaluation Exercise**
   - All participants evaluated demonstrated understanding of the IFU

Pending Labeling Comprehension Study

- Proposed participants: endocrinologists, primary care physicians, nurse practitioners, physician assistants
- Procedure:
  - Introduce the drug and the draft Prescribing Information-Dosage and Administration section
  - Read and perform knowledge tasks for 3 patient profiles
    - Pt Profile A: IDegLira as add on to oral diabetes medication(s)
    - Pt Profile B: converting to IDegLira from GLP-1 agonists
    - Pt Profile C: converting to IDegLira from basal insulin
  - Probe for subjective feedback if errors occur

Summary

- Human Factors data indicate that users were able to use the pen injectors
  - The errors that did occur are common for this device platform
- Data to determine prescriber ability to use the prescribing information to dose IDegLira is pending

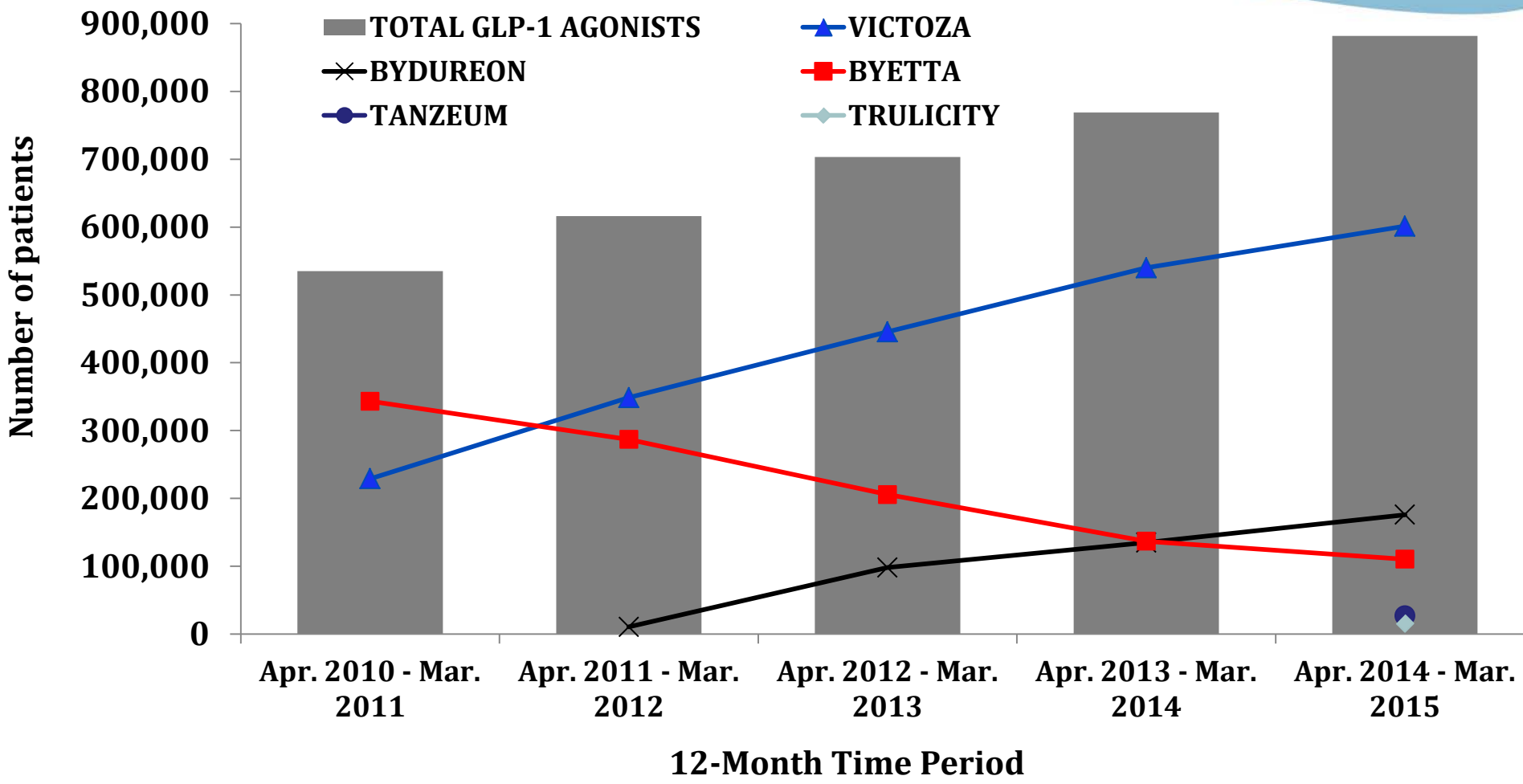
Backup Slides

National Utilization of GLP-1 Agonists
U.S. Outpatient Retail Pharmacies
April 2010 – March 2015

IMS Health, Vector One®: Total Patient Tracker (TPT)

- National-level projected audit designed to estimate unique patients receiving a dispensed prescription from outpatient retail pharmacies

GLP-1 Agonists: U.S. Outpatient Utilization



<u>Nationally estimated</u> number of patients who received a dispensed prescription for GLP-1 agonists, stratified by product, from U.S. outpatient retail pharmacies

Source: IMS Health: Vector One® Total Patient Tracker (TPT). April 2010-March 2015. Extracted March 2016.

Sample Concurrency Analysis of GLP-1 Agonists
April 2010 – March 2015

<u>*IMS Health*, Real-World Data (RWD) Adjudicated Claims – US database</u>

- Longitudinal patient-level health plan claims database capturing a sample of U.S. commercially insured patients
- Assessed the concurrent use of GLP-1 agonists and basal insulins

Discussion and Voting Questions

Endocrinologic and Metabolic Drugs Advisory Committee

May 24, 2016

1. Discussion

Discuss the benefit(s) of starting the fixed-combination drug product containing liraglutide and insulin degludec in patients with type 2 diabetes mellitus not treated with either a basal insulin or a GLP-1 agonist (i.e., starting two new drugs at once). In your discussion, identify the patient population in whom this use would be useful and address why you would select the fixed-combination product over use of an available GLP-1 agonist or basal insulin in these patients. Explain your rationale using data from the briefing materials and presentations, or from your own clinical experience.

2. Discussion

Discuss the benefit(s) of using the combination product containing liraglutide and degludec in patients with type 2 diabetes previously treated with either a basal insulin or a GLP-1 agonist (i.e., adding a single new drug to an existing regimen). In your answer, identify the patient population in whom use of the combination product in this manner would be useful. Explain your rationale using data from the briefing materials and presentations, or from your own clinical experience.

3. Discussion

Discuss clinical concerns related to the use of the fixed-combination product which combines a drug that, when used alone, has a wide effective dose range and is titrated to effect on a continuous scale (i.e., insulin degludec) with a drug that, when used alone, has one or two recommended effective dose(s) (i.e., liraglutide).

Specifically discuss:

- Issues related to loss of dosing flexibility including but not limited to: Use of potentially ineffective doses of one agent in populations with low insulin requirements, inability to dose the two drugs independently with the device presentation proposed, inability to increase the insulin dose beyond 50 units.
- Issues related specifically to product presentation/device including but not limited to: use errors that may occur in the care setting related to a lack of clarity on the amount of each product delivered with each given dose, insufficient understanding that, unlike insulin products, the maximum dose for the combination is capped.

4. Vote

Based on data in the briefing materials and presentations at today's meeting, do you recommend approval of the liraglutide/degludec fixed-combination drug, delivered using the proposed device, for the treatment of adult patients with type-2 diabetes mellitus?

a. If you voted yes, explain your rationale and discuss whether use of the combination should be approved for patients who have never been treated with a basal insulin product or a GLP-1 product, for patients who are inadequately controlled on either a basal insulin product or a GLP-1 product or for both populations. Recommend additional post-approval studies if you think these are needed.

b. If you voted no, explain your rationale and recommend additional pre-approval studies if you think these are needed.